The American Journal of Cardiology®

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DECEMBER 1, 1991

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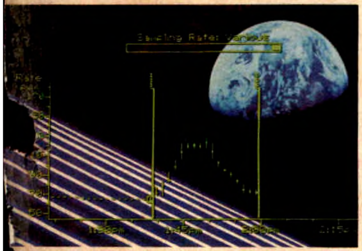

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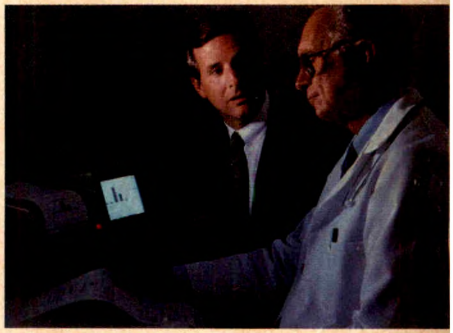

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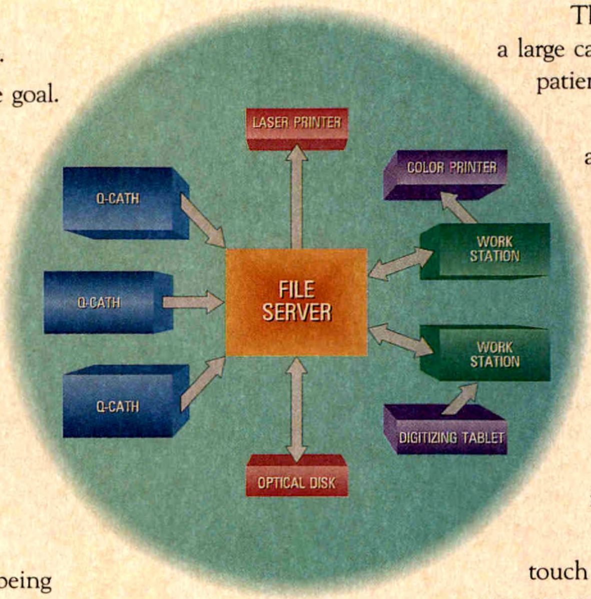

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DECEMBER 1, 1991, VOL.68, NO.15

CORONARY ARTERY DISEASE

1403

Relation Between Acute Ventricular Arrhythmias, Ventricular Late Potentials and Mortality in Acute Myocardial Infarction

Ma Hong, Thomas Peter, Werner Peters, Fang Z. Wang, Yuxu Xiu, Carol Vaughn, and Eli S. Gang

The relation between ventricular late potentials and acute ventricular tachycardia/fibrillation was studied in 281 survivors of uninterrupted acute myocardial infarction. The prevalence of late potentials was significantly higher in patients with than without ventricular tachycardia/fibrillation, and the incidence of ventricular tachycardia/fibrillation was higher among patients with late potentials. Patients with left bundle branch block were included in the study, although the definition of late potentials was modified in these cases. Multivariate analysis showed that late potentials and peak creatine kinase level were independently associated with early ventricular tachycardia/fibrillation. In-hospital mortality was significantly higher in the group with ventricular tachycardia/fibrillation, but 1-year mortality rates did not differ between the 2 groups. It is concluded that: (1) Late potentials are closely related to ventricular tachycardia/fibrillation in hyperacute and acute phases of infarction. (2) Presence of LBBB does not mitigate against the finding of late potentials in these patients. (3) Early ventricular tachycardia/fibrillation in acute infarction is related to large infarcts and a higher in-hospital mortality.

1410

Importance of Myocardial Infarct Artery Patency on the Prevalence of Ventricular Arrhythmia and Late Potentials After Thrombolysis in Acute Myocardial Infarction

Frank V. Aguirre, Morton J. Kern, Judith Hsia, Harvey Serota, Denise Janosik, Terry Greenwalt, Allan M. Ross, and Bernard R. Chaitman

Sixty-one patients with acute myocardial infarction who received intravenous recombinant tissue-type plasminogen activator, aspirin or heparin within 6 hours of symptom onset were studied to determine if early and sustained infarct artery patency after intravenous thrombolytic therapy influences myocardial electrical stability. Forty-eight patients (79%) had a patent infarct-related vessel and 13 (21%) patients had an occluded vessel. The mean number of ventricular premature beats per hour ($p < 0.01$) and late potential activity ($p < 0.03$) were significantly higher in patients with an occluded versus patent infarct-related vessel. These data

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suggest that successful thrombolysis decreases the prevalence of ventricular ectopic activity and late potentials in the early postinfarction phase. The reduction in both markers of electrical instability may help explain why the prognosis after successful thrombolysis is improved after acute myocardial infarction.

1417

Usefulness of QRST Time-Integral Values of 12-Lead Electrocardiograms in Diagnosing Healed Myocardial Infarction Complicated by Left Bundle Branch Block

Masayoshi Adachi, Hiroshi Hayashi, Makoto Hirai, Yasushi Tomita, Yoshio Ichihara, Akira Suzuki, Kazumasa Kondo, Haruo Inagaki, and Hidehiko Saito

We determined whether QRST time-integral values of 12-lead electrocardiograms would be useful in diagnosing myocardial infarction complicated by left bundle branch block. We calculated QRST time-integral values in each lead point of 12-lead electrocardiograms. The presence of myocardial infarction in patients with left bundle branch block was diagnosed with a high sensitivity and specificity by using QRST time-integral values in 12-lead electrocardiograms. With regard to localization of the myocardial infarction, the QRST time-integral values of precordial leads were useful in diagnosing an anterior myocardial infarction. However, it was difficult to localize an inferior myocardial infarction by using QRST time-integral values of inferior leads. This study demonstrates the practical usefulness of QRST time-integral values of 12-lead electrocardiograms in diagnosing myocardial infarction in the presence of left bundle branch block.

1425

Effects of High-Density Lipoprotein on Acetylcholine-Induced Coronary Vasoreactivity

Frederick E. Kuhn, Emile R. Mohler, Lowell F. Satler, Kathleen Reagan, David Y. Lu, and Charles E. Rackley

The relation between serum lipoproteins and acetylcholine-induced coronary vasoreactivity was investigated in patients ($n = 27$) undergoing coronary arteriography. The endothelium-dependent vasodilator acetylcholine reduced the diameter of both angiographically smooth ($13 \pm 4\%$, $p < 0.05$ vs baseline) and diseased ($19 \pm 4\%$, $p < 0.05$ vs baseline) coronary segments. A positive correlation was observed between high-density lipoprotein (HDL) cholesterol and normal response to acetylcholine in both angiographically smooth ($r = 0.59$, $p < 0.001$) and diseased ($r = 0.62$, $p < 0.02$) segments. However, no significant correlation was observed between total and low-density lipoprotein cholesterol, or between the total cholesterol to HDL ratio and the response of coronary artery diameter to acetylcholine infusion. These findings suggest that HDL cholesterol promotes normal endothelial cell function in both normal and atherosclerotic coronary segments.

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1431

Effects of Serum Lipid Levels on Restenosis After Coronary Angioplasty

Gregg J. Reis, Richard E. Kuntz, David I. Silverman, and Richard C. Pasternak

Serum lipid levels were measured prospectively in 186 patients who underwent successful coronary angioplasty. Fifty-nine patients (32%) developed clinical restenosis confirmed by angiography. Lipid levels were an independent predictor of restenosis. Patients with restenosis had higher baseline cholesterol/high-density lipoprotein (HDL) ratios and triglyceride levels. Among 90 patients with repeat lipid levels 6 months after angioplasty, significantly lower HDL cholesterol levels and higher cholesterol/HDL ratios were noted in patients with restenosis. The median follow-up cholesterol/HDL ratio of 5.5 divided groups with restenosis rates of 24% (ratio <5.5) and 55% (ratio >5.5). These data suggest that serum lipid levels are associated with the risk of clinical restenosis after angioplasty.

1436

Rationale and Design of a Secondary Prevention Trial of Lowering Normal Plasma Cholesterol Levels After Acute Myocardial Infarction: The Cholesterol and Recurrent Events Trial (CARE)

Frank M. Sacks, Marc A. Pfeffer, Lemuel Moye', Lisa E. Brown, Peggy Hamm, Thomas G. Cole, C. Morton Hawkins, and Eugene Braunwald

Recent clinical trials of primary and secondary prevention of cardiovascular disease have demonstrated that lowering plasma cholesterol decreases the incidence of coronary heart disease in patients with elevated plasma cholesterol. However, as reviewed in this article, it is not known whether patients with established coronary artery disease and normal plasma cholesterol can be benefited. The Cholesterol and Recurrent Events trial is testing whether pravastatin, a hydroxymethylglutaryl coenzyme A reductase inhibitor, will decrease the sum of fatal coronary heart disease and nonfatal myocardial infarction in patients who have recovered from myocardial infarction and who have normal plasma levels of total cholesterol (<240 mg/dl) and low-density lipoprotein cholesterol (115 to 174 mg/dl). The trial is enrolling 4,000 men and women from 80 centers throughout North America. The average duration of follow-up will be ≥5 years.

1447

Causes and Correlates of Death After Unsupported Coronary Angioplasty: Implications for Use of Angioplasty and Advanced Support Techniques in High-Risk Settings

Stephen G. Ellis, Richard K. Myler, Spencer B. King III, John S. Douglas, Jr., Eric J. Topol, Richard E. Shaw, Simon H. Stertzer, Gary S. Roubin, and Mary C. Murphy

To better understand the factors predisposing a patient to death after elective percutaneous transluminal coronary angioplasty (PTCA) and to gain insight into indications for high-risk PTCA both with and without

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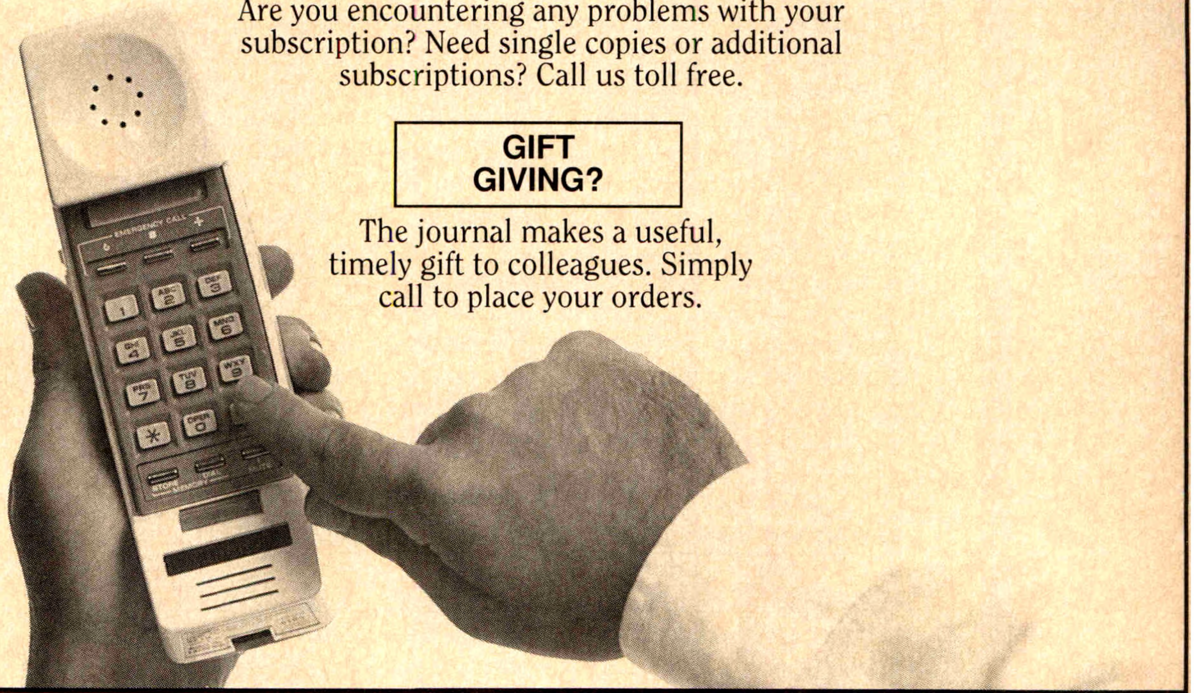

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adjunctive use of support devices, the outcomes of 8,052 consecutive procedures were reviewed. Cardiac death occurred after 26 procedures (0.3%). Left ventricular failure due to vessel closure at the dilated site, the most common cause of death, was independently correlated with female gender ($p < 0.001$), a "jeopardy score" ($p < 0.001$) and PTCA of a proximal right coronary artery site ($p = 0.002$), but not with left ventricular ejection fraction or presence of multivessel disease. Right ventricular failure after closure of the proximal right coronary artery, and left main coronary dissection accounted for the majority of the remaining deaths. These data highlight the superiority of the jeopardy score versus ejection fraction in the determination of risk and provide a framework for rational use of PTCA and support devices in the high-risk setting.

1452

Value of Transesophageal Echocardiography During Complex or High-Risk Coronary Interventions in the Cardiac Catheterization Laboratory

Gregory S. Pavlides, Andrew M. Hauser, Patricia I. Dudlets, Steven L. Almany, Cindy L. Grines, and William W. O'Neill

The feasibility and value of transesophageal echocardiography (TEE) during complex or high-risk coronary intervention was studied in 53 cases. The primary imaging goals were left ventricular monitoring in 39 patients (74%), left main coronary artery (LMCA) imaging in 9 patients (17%) and both in 5 patients (9%), and these were achieved in 51 patients (96%). Left ventricular monitoring was accomplished in 43 patients. In 25 (58%) of these, important observations were provided by TEE, which were not apparent by symptoms, or hemodynamic, electrocardiographic and radiographic monitoring. Management of the interventional procedure was influenced by TEE in 11 patients (26%). In 11 of the 13 patients whose LMCA was visualized, stenotic lesion diameter by TEE correlated well with quantitative angiography both before ($r = 0.83$, standard error of the estimate $= 0.01$, $p < 0.002$) and after ($r = 0.80$, standard error of the estimate $= 0.03$, $p < 0.005$) intervention. Thus, TEE during complex or high-risk coronary intervention is a feasible, safe and valuable tool for rapid detection of altered myocardial function and may influence clinical decision making during the interventional procedure. In patients undergoing LMCA intervention, TEE accurately measures stenotic lesion diameter, providing a potential noninvasive means for future follow-up.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1458

Effects of Cardiac Denervation on Atrioventricular Nodal Accommodation and Hysteresis

Bryan E. Fuhs and Kenneth A. Ellenbogen

Atrioventricular (AV) nodal accommodation (the time-dependent change in AV nodal conduction after a sudden change in atrial pacing cycle length) and AV nodal hysteresis (the asymmetry of AV nodal accommodation following directionally opposite atrial pacing cycle length changes) have been well characterized in humans. To determine if cardiac trans-

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plantation alters AV nodal accommodation and hysteresis, the responses of 13 patients after orthotopic cardiac transplantation were compared with responses in 12 control patients. The cardiac transplant patients demonstrated 1.5 ± 1.3 beats of hysteresis, and the control patients 2.1 ± 1.4 beats (p = not significant). Cardiac transplant and control patients behaved in a similar fashion, suggesting that neural influences at rest are not primarily responsible for AV nodal accommodation.

CONGESTIVE HEART FAILURE

1465

Initial Blood Pressure Response to Enalapril in Hospitalized Patients (Studies of Left Ventricular Dysfunction [SOLVD])

William B. Hood, Jr., Marston Youngblood, Jalal K. Ghali, Marette Reid, William J. Rogers, Donna Howe, Koon K. Teo, and Thierry H. LeJemtel, for the SOLVD Investigators

Studies of Left Ventricular Dysfunction (SOLVD) is a randomized trial of enalapril versus placebo in reducing mortality in patients with cardiac dysfunction (ejection fraction ≤35%). Before randomization, 89 patients at risk for hypotension (1.2% of the total screened) were hospitalized and administered 2.5 mg of enalapril orally at baseline and again 12 hours later. Baseline systolic and diastolic blood pressures were 115 ± 18 and 73 ± 10 mm Hg, respectively. After enalapril, systolic blood pressure decreased significantly 8 to 20 hours after the initial dose (mean reduction 8 to 11 mm Hg). Symptoms relating to decrease in blood pressure were noted in 13 patients (15%). Most patients with cardiac dysfunction readily tolerate enalapril. However, the agent should be administered with caution to patients with advanced congestive failure and diminished baseline blood pressure.

VALVULAR HEART DISEASE

1469

Systemic and Left Ventricular Responses to Exercise Stress in Asymptomatic Patients with Valvular Aortic Stenosis

Christopher A. Clyne, James A. Arrighi, Barry J. Maron, Vasken Dilsizian, Robert O. Bonow, and Richard O. Cannon III

The exercise responses of 14 asymptomatic patients with significant aortic stenosis were assessed with Doppler echocardiography. Compared with age- and sex-matched control subjects, patients had reduced exercise tolerance and maximal oxygen consumption associated with decreased peak systolic blood pressure response, and less of an increase in left ventricular ejection fraction, with a decrease in end-diastolic and stroke volumes from baseline measurements. Thus, despite the absence of symptoms patients with aortic stenosis demonstrate limited tolerance, and abnormal systemic and left ventricular hemodynamics during exercise stress.

1477

Doppler Echocardiographic Findings in Adults With Severe Symptomatic Valvular Aortic Stenosis

Catherine M. Otto, Rick A. Nishimura, Kathryn B. Davis, Katherine B. Kisslo, Thomas B. Bashore, and the Balloon Valvuloplasty Registry Echocardiographers

Echocardiographic data in 680 adults undergoing balloon aortic valvuloplasty showed marked variability in aortic stenosis severity and a high prevalence (54%) of ventricular systolic dysfunction. Left ventricular outflow tract diameter poorly correlated with body size. Mean pressure gradient was closely related to maximal jet velocity (mean $\Delta P = 2.4V^2 + 0.75$ mm Hg) and the ratio of velocities in the outflow tract to aortic jet correlated with Doppler ($r = 0.67$) and invasive valve areas ($r = 0.40$). It is concluded that although measurement of outflow tract diameter in each patient is needed for valve area calculations, simpler echocardiographic measures may be helpful in evaluating valvular stenosis severity.

1485

Doppler Echocardiographic Estimation of Mitral Valve Area During Changing Hemodynamic Conditions

Alan C. Braverman, James D. Thomas, and Richard T. Lee

To compare the continuity equation and pressure half-time methods of mitral valve area (MVA) determination under changing hemodynamic conditions, 17 patients with symptomatic rheumatic mitral stenosis underwent Doppler echocardiography at rest and during minor supine bicycle exercise. Mean MVA by the Gorlin formula at catheterization was 0.9 ± 0.4 cm^2. Cardiac output and transmitral gradient increased with exercise ($p < 0.001$), while the net atrioventricular compliance decreased significantly ($p < 0.001$). MVA by the pressure half-time method increased significantly during exercise from 1.0 ± 0.2 to 1.4 ± 0.4 cm^2. With use of the continuity equation method, MVA remained constant from rest to exercise at 0.8 ± 0.3 cm^2 ($p = 0.83$). The data suggest that during periods of changing hemodynamics, the continuity equation method of determining MVA may be preferable to the pressure half-time method.

CONGENITAL HEART DISEASE

1491

Late Results (30 to 35 Years) After Operative Closure of Isolated Ventricular Septal Defect from 1954 to 1960

James H. Moller, Ceeya Patton, Richard L. Varco, and C. Walton Lillehei

The current status of 296 consecutive surviving patients of surgical closure of a ventricular septal defect operated on from 1954 to 1960 was determined. Of the 290 available patients, 59 (20%) have died, with more deaths occurring among those with elevated pulmonary vascular resistance, those operated after age 2 years and those with heart block. Most of the 230 surviving patients are in New York Heart Association class I, and few have medical problems related to their cardiac malformations. These good results of patients operated on during an early era of cardiac surgery

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should be useful to physicians treating adults who have undergone cardiac surgery during childhood. The data support the trend toward surgery for patients with ventricular septal defects at an early age, and confirm the concern about elevated pulmonary vascular resistance before surgery, and conduction abnormalities after surgery.

1498

Comparison of Transcranial Doppler Ultrasound and Transesophageal Contrast Echocardiography in the Detection of Interatrial Right-to-Left Shunts

James J. Nemec, Thomas H. Marwick, Ronald J. Lorig, Malcolm B. Davison, Marc I. Chimowitz, Harvey Litowitz, and Ernesto E. Salcedo

The efficacy of transcranial Doppler ultrasound and transthoracic contrast echocardiography for detection of an interatrial right-to-left shunt was assessed using transesophageal contrast echocardiography in 32 subjects. Transcranial Doppler had a sensitivity, specificity and accuracy of 100% for predicting an interatrial right-to-left shunt by transesophageal contrast echocardiography. In comparison, transthoracic contrast echocardiography had a sensitivity of 54%, specificity of 94% and accuracy of 77%. Transcranial Doppler is accurate for the detection of an interatrial right-to-left shunt and may be useful as an alternative to transesophageal echocardiography, where the primary indication for transesophageal study is exclusion of an interatrial right-to-left shunt.

MISCELLANEOUS

1503

Effect of Digoxin on ST-Segment Changes Detected by Ambulatory Electrocardiographic Monitoring in Healthy Subjects

Aryan N. Mooss, John A. Prevedel, Syed M. Mohiuddin, Daniel E. Hilleman, and Michael H. Sketch, Sr.

Fifty healthy male subjects received digoxin 0.25 mg/day for 14 days. Ambulatory electrocardiographic monitoring and exercise stress testing was performed before and on the fourteenth day of digoxin therapy. During therapy, 13 (26%) subjects had at least 1 episode of ST depression and 5 (10%) subjects had multiple episodes of ST depression detected by ambulatory monitoring. Ten (20%) subjects had ST depression during exercise stress. Three (6%) had ST depression that occurred only at times other than during the stress test. Digoxin causes false-positive ST-segment depression detected by ambulatory monitoring. The incidence is similar to that observed during stress testing, but also occurs at heart rates lower than that achieved during exercise testing.

1507

Two-Dimensional Contrast Echocardiography in the Detection and Follow-Up of Congenital Pulmonary Arteriovenous Malformations

Benico Barzilai, Alan D. Waggoner, Cheryl Spessert, Daniel Picus, and Daniel Goodenberger

Pulmonary arteriovenous (A-V) malformation is a frequent manifestation in patients with hereditary hemorrhagic telangiectasia. Contrast 2-dimensional echocardiography was used to identify 14 patients with A-V malformation and 10 with atrial right-to-left shunt. Patients with A-V malformation had a significant ($p < 0.001$) delay in left atrial appearance of venous injections of agitated saline solution compared with those with atrial right-to-left shunt. Eleven patients with A-V malformation underwent pulmonary angiography. Contrast 2-dimensional echocardiography demonstrated 3 to 4+ opacification of the left ventricular chamber ($n = 8$) in patients with large or multiple A-V malformations, whereas patients with small A-V malformation ($n = 3$) had contrast 2-dimensional echocardiographic findings of 1 to 2+ left ventricular opacification. After embolotherapy of A-V malformation, immediate follow-up contrast 2-dimensional echocardiography revealed diminution of right-to-left shunt in 9 patients, but a significant residual intrapulmonary right-to-left shunt was detected in 2 and necessitated repeat pulmonary angiography with embolotherapy of a previously undetected A-V malformation. Contrast 2-dimensional echocardiography is extremely sensitive for identification and follow-up of pulmonary A-V malformation.

1511

Cardiac Myocytes and Dendritic Cells Harbor Human Immunodeficiency Virus in Infected Patients With and Without Cardiac Dysfunction: Detection by Multiplex, Nested, Polymerase Chain Reaction in Individually Microdissected Cells from Right Ventricular Endomyocardial Biopsy Tissue

E. Rene Rodriguez, Suhail Nasim, Judith Hsia, Ramón L. Sandin, Andrea Ferreira, Betty A. Hilliard, Allan M. Ross, and Carleton T. Garrett

Fifteen of 215 human immunodeficiency virus (HIV)-infected patients studied underwent endomyocardial biopsy; 5 had cardiovascular symptoms and 10 did not. HIV sequences for gag and pol genes were amplified in microdissected myocytes or dendritic cells by a multiplex, nested polymerase chain reaction. HIV was amplified from myocytes of 2 of 5 symptomatic and 6 of 10 asymptomatic patients. Dendritic cells had HIV in 5 of 5 symptomatic and in 8 of 10 asymptomatic patients. Thus, symptomatic HIV cardiac dysfunction did not appear to be due to a direct role of HIV on the cardiac myocytes.

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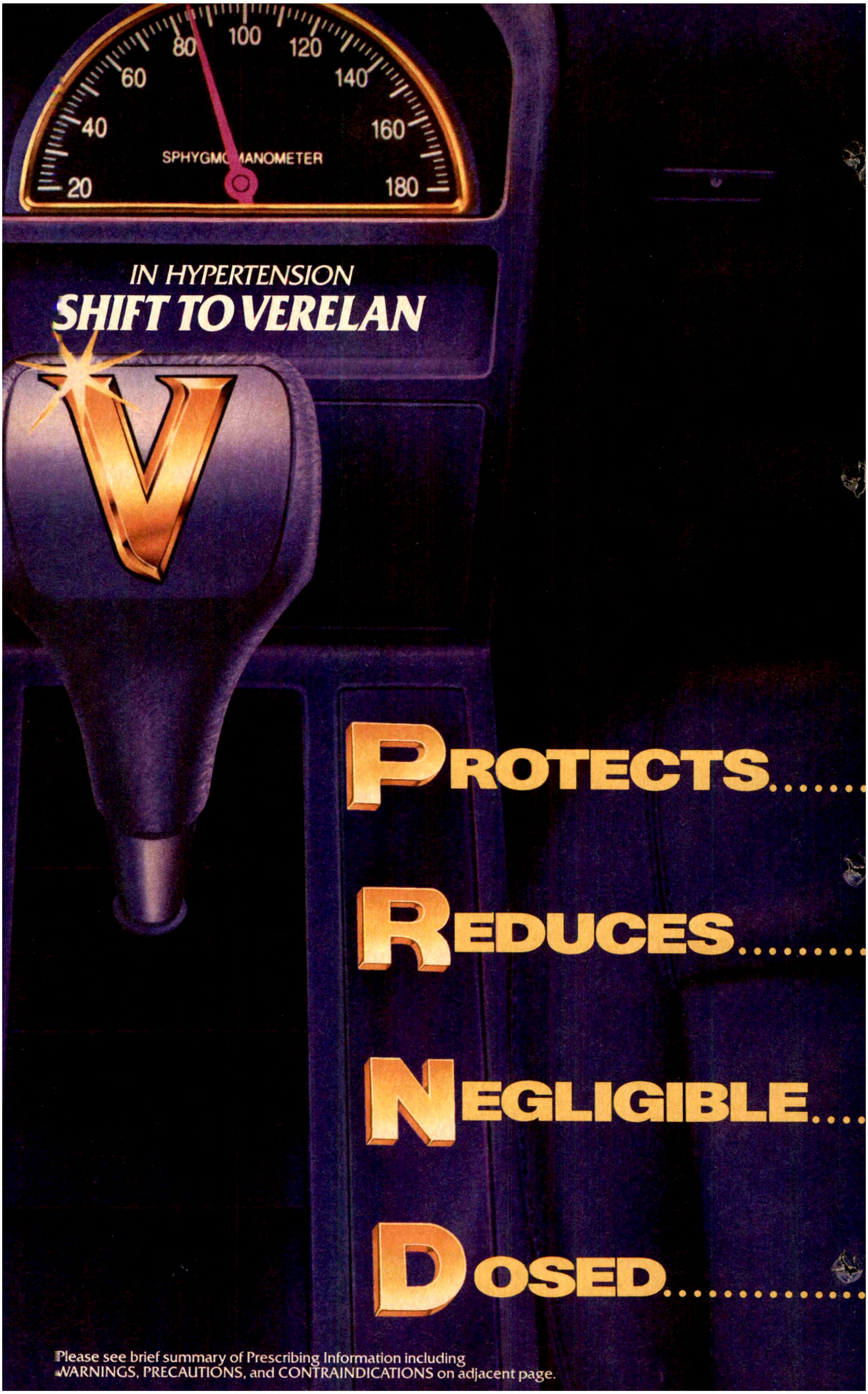

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CORONARY ARTERY DISEASE

The American Journal of Cardiology

DECEMBER 1, 1991, VOL. 68, NO. 15

Relation Between Acute Ventricular Arrhythmias, Ventricular Late Potentials and Mortality in Acute Myocardial Infarction

Ma Hong, MD, Thomas Peter, MD, Werner Peters, MD, Fang Z. Wang, MD,
Yuxu Xiu, MD, Carol Vaughn, RN, and Eli S. Gang, MD

The relation between ventricular late potentials and the occurrence of acute (in-hospital) and hyperacute (before hospital admission) ventricular tachycardia or fibrillation was studied in 281 consecutive patients with uninterrupted acute myocardial infarction. The prevalence of late potentials was significantly higher in patients with than without ventricular tachycardia/fibrillation (65 vs 22%; p <0.01). These relations persisted among patients with left bundle branch block, although a different definition was used for identifying late potentials in these patients. Multivariate analysis showed that presence of late potentials and peak creatine kinase enzyme level were the only 2 independent variables associated with early ventricular tachycardia/fibrillation.

Total in-hospital mortality, as well as in-hospital cardiac mortality, was significantly higher among patients with than without acute ventricular tachycardia/fibrillation. However, at 1 year, mortality rates did not differ between the 2 groups.

The following conclusions were drawn from this study: (1) Late potentials are closely related to ventricular tachycardia/fibrillation in hyperacute and acute phases of infarction. (2) Presence of left bundle branch block does not mitigate against the finding of late potentials in these patients. (3) Early ventricular tachycardia/fibrillation in acute infarction is related to large infarctions and to a high in-hospital mortality rate.

(Am J Cardiol 1991;68:1403–1409)

Several clinical studies have shown that the presence of ventricular late potentials on signal-averaged electrocardiography identifies patients at high-risk for incurring fatal ventricular tachyarrhythmias in the late phase of myocardial infarction.[1-10] Much less is known about the relation between late potentials and ventricular tachyarrhythmias in the acute phase of myocardial infarction. Studies on the subject are few, and conflicting conclusions have been drawn from relatively small patient groups.[11-15] In keeping with these observations, we conducted this study to: (1) assess the prevalence of late potentials in the acute phase of uninterrupted myocardial infarction; and (2) examine the relation between late potentials, clinical variables and ventricular tachyarrhythmias in acute myocardial infarction.

METHODS

Patients: We recruited 391 consecutive patients admitted to the cardiac care unit of the Cedars-Sinai Medical Center with documented acute myocardial infarction from November 1986 to February 1988. Patients were excluded by the following prospectively defined exclusion criteria: (1) those who received acute thrombolytic therapy (n = 64); (2) those who underwent coronary angioplasty or bypass surgery, or both, before undergoing signal-averaged electrocardiography (n = 25); and (3) those with right bundle branch block (n = 21). In all, 281 patients without right bundle branch block who had uninterrupted myocardial infarction were enrolled in this prospective study. Diagnosis

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TABLE I Clinical Characteristics of 281 Patients, and Relation to Presence of Ventricular Arrhythmias

	VT/VF (n = 26)	No VT/VF (n = 255)	p Value
Age (years)	72 ± 9	73 ± 11	NS
Men	17/26 (65%)	169/255 (66%)	NS
Prior infarction	13/26 (50%)	90/255 (35%)	NS
Peak CK (IU/liter)	3,380 ± 3,297	949 ± 781	<0.001
Peak CK-MB (IU/liter)	227 ± 245	99 ± 92	<0.05
Killip class ≥2	13/26 (50%)	99/255 (39%)	NS
Heart enlarged	14/26(54%)	110/255 (43%)	NS
Infarct site			NS
Anterior	12/26 (46%)	70/255 (28%)	
Inferior	6/26 (23%)	59/255 (23%)	
Non-Q wave	6/26 (23%)	105/255 (41%)	
Not determined	2/26 (8%)	21/255 (8%)	
Left ventricular ejection fraction (%)	32 ± 10	43 ± 14	<0.01
Late potentials	17/26 (65%)	56/255 (22%)	<0.0001

CK = creatine kinase; NS = not significant; VT/VF = ventricular tachycardia/fibrillation.

of acute myocardial infarction was based on clinical symptoms developing electrocardiographic changes with or without development of pathologic Q waves, and serial elevation of total creatine kinase and its MB isoenzyme levels.

Acute ventricular arrhythmias were defined as spontaneous sustained ventricular tachycardia or primary ventricular fibrillation occurring in the hyperacute or acute phase of myocardial infarction (i.e., either before hospital admission or within the first 10 days of admission). Ventricular tachycardia was defined as spontaneous tachycardia of ventricular origin, with rates >130 beats/min and lasting ≥30 seconds or requiring termination because of hemodynamic decompensation.

Signal-averaged electrocardiography: All patients had ≥1 signal-averaged electrocardiographic recording in the hospital within the first 10 days (first recording performed at 3 ± 2 days). The quantitative signal-processing method used was that of Simson.[1] Visual confirmation of the measurements of QRS duration was obtained in each case by 2 investigators. Late potentials were defined as root-mean-square voltage ≤25 uV in the last 40 ms of the QRS complex or total filtered QRS duration ≥120 ms, or both. For those patients with an unfiltered QRS duration ≥110 ms (nonspecific intraventricular conduction delay or left bundle branch block), late potentials were defined only as root-mean-square voltage ≤20 uV in the last 40 ms of the QRS complex. In patients who had ≥1 signal-averaged electrocardiographic tracing when late potentials were consistently present or absent, the first tracings were used for analysis. When the serial tracings were discrepant, the first positive late potential tracings were used. Duration of low-amplitude signal <40 uV was analyzed, but was not used as a definition criterion.

Statistical analysis: Continuous variables were compared using Student's unpaired *t* test, and categorical data were compared using the chi-square or Yates' correction of the chi-square test. Stepwise multiple logistic regression analyses were performed, with ventricular tachycardia/fibrillation in various phases of acute myocardial infarction (see later) as the dependent variable and with the clinical descriptors listed in Table I as the independent variables. Because a measure of left ventricular ejection fraction was available in only 166 patients (in only 13 of 26 with ventricular arrhythmias), this variable was not entered in the multivariate analyses. Statistical significance was set at a 2-tailed p value <0.05.

RESULTS

Patient population: Of 281 patients, 26 had a documented episode of ventricular tachycardia/fibrillation within the first 10 days of acute myocardial infarction. The 26 patients were subdivided as follows: 12 with ventricular tachycardia/fibrillation in the hyperacute (before hospital) phase (subgroup 1); and 14 in the acute (in-hospital) phase (subgroup 2). All patients with hyperacute arrhythmias met our definition of acute infarction. In keeping with published studies that have examined patients with early ventricular tachycardia/fibrillation after acute myocardial infarction,[16,17] we further categorized 21 out of the 26 patients as those with ventricular tachycardia/fibrillation that occurred within 48 hours of myocardial infarction (subgroup 3). As shown in Figure 1, ventricular arrhythmia was ventricular fibrillation in 14 patients, and most patients (13 of 14) had ventricular fibrillation within 48 hours of acute myocardial infarction. All episodes of ventricular fibrillation and 2 of 12 episodes of ventricular tachycardia were cardioverted with direct current shock. The other 10 patients with ventricular tachycardia were treated with intravenous lidocaine or procainamide.

The patients' clinical characteristics are listed in Table I. Univariate analysis showed that creatine kinase and its MB isoenzyme values were significantly higher, and left ventricular ejection fraction was significantly lower in the group with than that without ventricular arrhythmias. Table II lists the clinical characteristics exclusively in patients who had ventricular arrhythmias within 48 hours after onset of myocardial infarction (subgroup 3) compared with those without ventricular arrhythmias; the similarities and differences between the 2 groups persist.

The mean time after infarction at which the first signal-averaging was performed was the same in groups with and without ventricular arrhythmias (3 ± 2 days). Two or more studies were done in 90% of patients with-

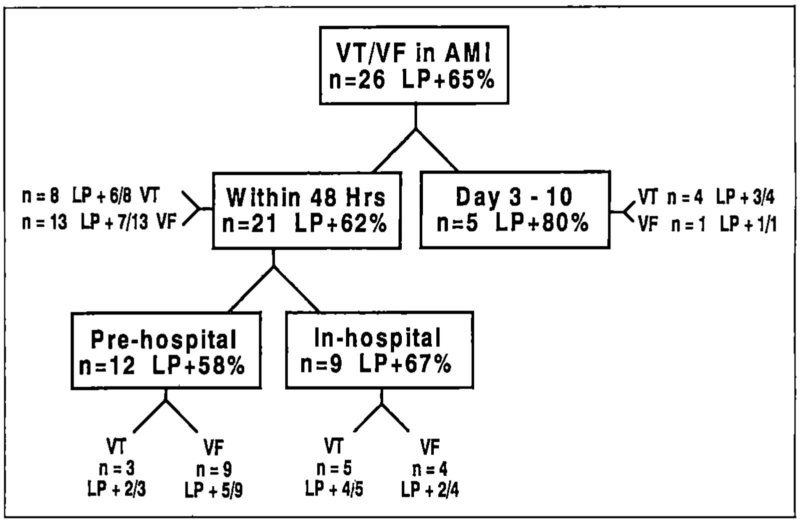

FIGURE 1. Chart displaying time of ventricular arrhythmias in acute infarction (AMI), and prevalence of ventricular late potentials (LP). VF = ventricular fibrillation; VT = ventricular tachycardia; + = presence; – = absence.

in the first 10 days of myocardial infarction. The average number of studies was similar between patients with and without ventricular arrhythmias (3 ± 1). The first signal-averaging was performed after the episode of ventricular arrhythmias in 21 of 26 patients.

Prevalence of late potentials: The overall prevalence of late potentials among the 281 study patients was 26% (73 patients). As shown in Table I, a significantly higher prevalence of late potentials was seen in patients with than without ventricular arrhythmias (65 vs 22%; $p < 0.0001$). Conversely, of 73 patients with late potentials, 23% developed hyperacute or acute phase ventricular arrhythmias, whereas of the remaining 208 patients with no late potentials, only 4% developed ventricular arrhythmias ($p < 0.0001$). Thus, the prevalence of ventricular arrhythmias was nearly 6 times higher in patients with late potentials (Figure 2).

TABLE II Clinical Characteristics in Patients With and Without Ventricular Arrhythmias Within 48 Hours of Myocardial Infarction

	VT/VF Within 48 Hours		
	+ (n = 21)	– (n = 255)	p Value
Age (years)	70 ± 10	73 ± 11	NS
Men	15/21 (71%)	169/255 (66%)	NS
Prior infarction	9/21 (43%)	90/255 (35%)	NS
Peak CK (IU/liter)	3,618 ± 3,579	949 ± 781	<0.01
Peak CK-MB (IU-liter)	238 ± 262	99 ± 92	<0.05
Killip class > 2	10/21 (48%)	99/255 (39%)	NS
Heart enlarged	10/21 (48%)	110/255 (43%)	NS
Infarct site			NS
Anterior	10/21 (47%)	70/255 (28%)	
Inferior	4/21 (19%)	59/255 (23%)	
Non-Q wave	5/21 (24%)	105/255 (41%)	
Not determined	2/21 (10%)	21/255 (8%)	
Left ventricular ejection fraction (%)	34 ± 10	43 ± 13	<0.05
Late potentials	13/21 (62%)	56/255 (22%)	<0.0001

+ = presence; – = absence; other abbreviations as in Table I.

The prevalence of late potentials in different subgroups with ventricular arrhythmias was as follows: 58% (7 of 12 patients) in subgroup 1; 71% (10 of 14) in subgroup 2; and 62% (13 of 21) in subgroup 3. The prevalence of late potentials in all these subgroups of patients was significantly higher than in patients without ventricular arrhythmias ($p < 0.05$, $p < 0.01$ and $p < 0.01$, respectively). Late potentials were seen with equal frequency in both types of ventricular arrhythmias (i.e., in 70% of patients with ventricular tachycardia and in 57% with ventricular fibrillation; $p > 0.05$). For identification of ventricular tachycardia/fibrillation occurring in the hyperacute/acute phase of myocardial infarction, late potentials had a sensitivity of 65% and a specificity of 78, whereas the predictive accuracy of a positive test was 23 and that of a negative test was 96.

Signal-averaged electrocardiographic indexes: Patients with ventricular arrhythmias in various phases of acute myocardial infarction (all 26 patients with ventricular arrhythmias, and those with ventricular arrhythmias in subgroups 1 and 3) were compared with those without ventricular arrhythmias to determine if there were significant differences in the values of the

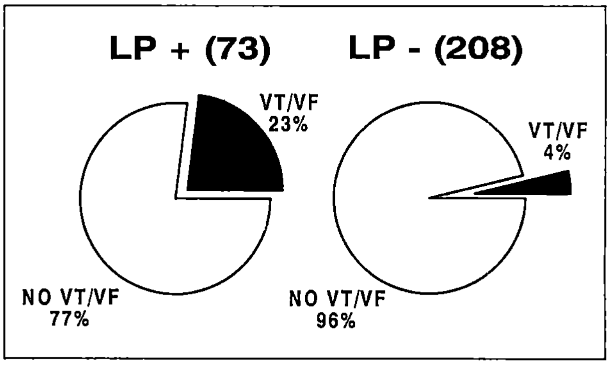

FIGURE 2. Pie diagram showing incidence of early ventricular tachycardia/fibrillation (VT/VF) among patients with and without ventricular late potentials (LP).

signal-averaged electrocardiographic indexes. Results are listed in Tables III and IV.

Analysis of patients with left bundle branch block (Figure 3): A left bundle branch block pattern was recorded in 29 study patients (6 of the 26 patients with early ventricular arrhythmias and 23 of 255 without ventricular arrhythmias). As shown in Figure 4, late potentials were frequently recorded in patients with ventricular arrhythmias irrespective of whether a left bundle branch block pattern was seen. The data in Table III also show significant differences in 3 of 4 signal-averaged electrocardiographic indexes.

Stepwise multiple logistic regression analysis: The analyses compared the 255 patients without ventricular arrhythmias with (a) all 26 with ventricular arrhythmias, (b) the 12 in subgroup 1, and (c) the 21 in sub-

TABLE III Signal-Averaged Electrocardiographic Parameters in Patients With and Without Early Ventricular Arrhythmias

	No Left Bundle Branch Block			Left Bundle Branch Block		
	VT/VF (n = 20)	No VT/VF (n = 232)	p Value	VT/VF (n = 6)	No VT/VF (n = 23)	p Value
Unfiltered QRS (ms)	101 ± 12	98 ± 4	NS	157 ± 9	142 ± 22	NS
Filtered QRS (ms)	116 ± 14	104 ± 16	<0.001	164 ± 9	147 ± 23	<0.05
D40 (ms)	37 ± 17	25 ± 12	<0.001	42 ± 10	23 ± 17	<0.05
RMSV40 (uV)	30 ± 21	85 ± 70	<0.0001	19 ± 4	53 ± 46	<0.01

D40 = duration of low-amplitude signals <40 uV; RMSV40 = root-mean-square voltage of signals in last 40 ms of QRS complex; other abbreviations as in Table I.

TABLE IV Signal-Averaged Electrocardiographic Parameters in Patients with Ventricular Arrhythmias in Subgroups 1 and 3 (patients with left bundle branch block were excluded)

	VT/VF* (n = 16)		No VT/VF (n = 232)		VT/VF** (n = 8)
Unfiltered QRS (ms)	99 ± 12	NS	98 ± 232	NS	104 ± 10
Filtered QRS (ms)	114 ± 14	p <0.05	104 ± 16	p <0.05	117 ± 11
D40 (ms)	38 ± 17	p <0.001	25 ± 12	p <0.005	36 ± 11
RMSV40 (uV)	33 ± 22	p <0.0001	85 ± 70	p <0.0001	33 ± 21

* = subgroup 3; ** = subgroup 1.
Abbreviations as in Tables I and III.

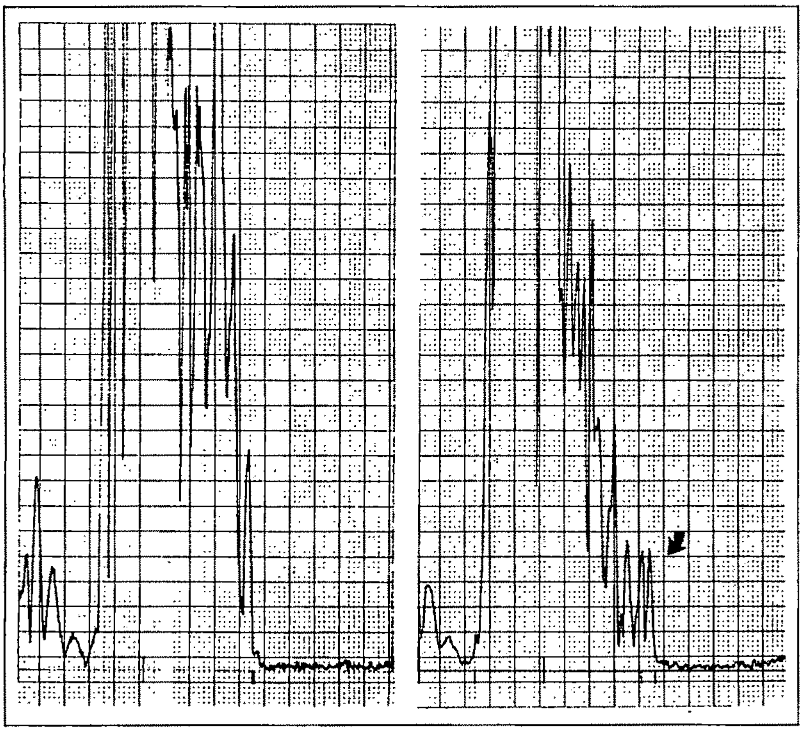

FIGURE 3. Illustrations of presence and absence of ventricular late potentials in patients with left bundle branch block pattern. *Left,* terminal root-mean-square voltage is 72 uV, and no visible late potentials are present. *Right,* late potentials are visible *(arrow),* and terminal voltage is 17 uV.

group 3. All clinical variables listed in Table I (except left ventricular ejection fraction) were used in these analyses. In each of these subgroups, the only 2 independent variables associated with early ventricular arrhythmias were peak creatine kinase level and presence of ventricular late potentials. When creatine kinase level was dichotomized at ≥1500 IU/liter, and its MB isoenzyme at ≥150 IU/liter, the presence of ventricular late potentials was the most significant independent variable associated with early ventricular arrhythmias, followed by peak creatine kinase ≥1500 IU/liter.

In-hospital and long-term mortality: IN-HOSPITAL DEATH: The total in-hospital mortality rate was 31% (8 of 26) in patients with ventricular arrhythmias, and 6% (15 of 255) in those without ventricular arrhythmias ($p < 0.0001$). The cardiac mortality rates were 27 (7 of 26) and 5% (13 of 255) in patients with and without ventricular arrhythmias ($p < 0.0001$). Of 21 patients with ventricular arrhythmias within the first 48 hours of myocardial infarction, 5 patients whose presenting arrhythmia was ventricular fibrillation died. Four of these patients died from cardiac causes (2 cardiogenic shock, 1 pulmonary edema and 1 recurrent ventricular fibrillation). Thus, among 13 patients with ventricular fibrillation developing within the first 48 hours, the total in-hospital mortality rate was 38% (5 of 13), and cardiac mortality was 31% (4 of 13). Both total and cardiac mortality rates were significantly higher in patients with ventricular arrhythmias within 48 hours than in those without ventricular arrhythmias (38 vs 6%, $p < 0.0001$, and 31 vs 5%, $p < 0.001$, respectively).

ONE-YEAR FOLLOW-UP: One-year follow-up data were available for all patients with early arrhythmias and for 98% of those without ventricular arrhythmias who left the hospital alive (18 of 18 and 236 of 240, respectively). We concluded that: (1) Total and cardiac deaths were higher among patients with ventricular arrhythmias, but the differences did not reach statistical significance (7 of 18 [39%] vs 45 of 236 [19%] for total deaths; 5 of 18 [28%] vs 26 of 236 [11%] for cardiac deaths). (2) Similarly, 1-year mortality of patients presenting with acute ventricular fibrillation (3 of 8, 38%) did not differ from that of those without acute ventricular fibrillation (19%). (3) In contrast, 1-year sudden death mortality was higher in patients presenting with ventricular arrhythmias (5 of 18 [28%] vs 13 of 236 [6%]; $p < 0.01$). (4) Late potentials had been recorded in 10 of 18 (56%) patients who had sudden death during the first year.

DISCUSSION

The salient points of our study are as follows: (1) Ventricular late potentials have an independent and significant association with the occurrence of acute ventricular tachycardia/fibrillation in the setting of acute myocardial infarction. (2) Presence of left bundle branch block does not mitigate against the finding of late potentials by signal-averaged electrocardiography in acute myocardial infarction. (3) Presence of ventricular tachycardia/fibrillation in the early phases of acute myocardial infarction is associated with large infarctions and with high in-hospital mortality rate.

Prevalence of late potentials in acute myocardial infarction: Our study showed a 26% prevalence rate of ventricular late potentials recorded 3 ± 2 days after myocardial infarction. Other studies have shown a prevalence ranging from 16 to 58%,[2,10-15] but patient populations varied among different studies. For example, successful thrombolytic treatment is associated with a marked reduction in the prevalence of late potentials in acute myocardial infarction.[18-20] We took special care to exclude all patients with thrombolytic treatment. Furthermore, although no studies have yet reported decreased prevalence of late potentials after coronary angioplasty in acute myocardial infarction, 1 report found that in patients with previous myocardial

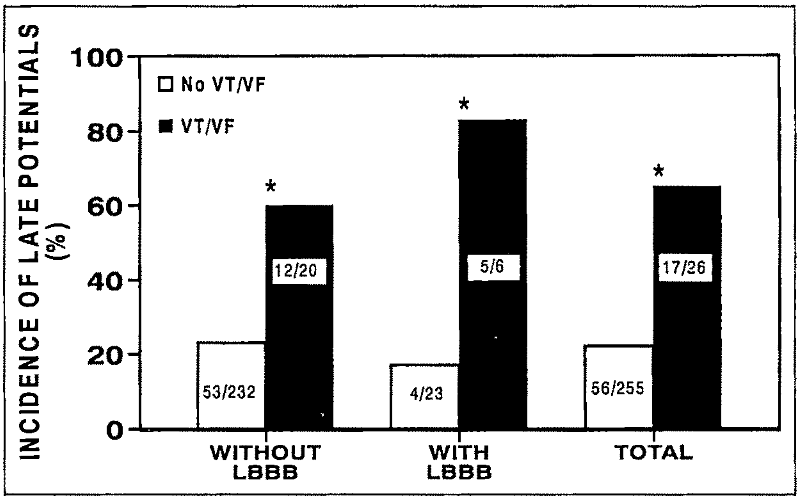

FIGURE 4. Prevalence of ventricular late potentials in patients with and without left bundle branch block (LBBB). VT/VF = ventricular tachycardia/fibrillation; *p <0.01.

infarction, 39% lost their late potentials after coronary bypass surgery, and in all patients, the mean value of signal-averaged electrocardiographic variables improved after bypass surgery.[21] Thus, for the purpose of this study we excluded all patients with coronary bypass surgery or angioplasty, or both, performed within 3 days before a signal-averaging study. Therefore, the present study can be regarded as a reasonable assessment of the prevalence of late potentials in consecutive patients with uninterrupted natural history of acute myocardial infarction.

Late potentials and hyperacute or acute phase ventricular tachyarrhythmias in myocardial infarction: The relation between late potentials and ventricular tachycardia/fibrillation occurring in the hyperacute or acute phase of myocardial infarction remains inadequately studied in a large number of consecutive patients. Some investigators[11,14,22] have suggested that late potentials do not predict the occurrence of in-hospital phase ventricular tachyarrhythmias in patients with acute myocardial infarction. In contrast, 1 study[15] has suggested that late potentials are a useful predictor of ventricular arrhythmias and sudden death 24 hours after acute myocardial infarction, but not of ventricular fibrillation occurring within the first 24 hours. Furthermore, 2 other studies[12,13] have suggested that the presence of late potentials can indeed identify ventricular tachyarrhythmias occurring within the first 24 hours after acute myocardial infarction.

Our study demonstrates that late potentials are associated with ventricular tachycardia/fibrillation no matter when the arrhythmia occurred (in the hyperacute phase, or within the first 48 hours of myocardial infarction or the first 10 days in the hospital). This information might enable clinicians to stratify patients into low- and high-risk groups for acute phase ventricular arrhythmias, and longer monitoring before discharge from the cardiac care unit may be warranted in the high-risk group.

Experimental basis for ventricular late potentials in the acute phase of myocardial infarction: Acute experimental ischemia is associated with a high prevalence of ventricular tachycardia and fibrillation,[23] as well as with delayed and fractionated electrograms recorded directly from ischemic myocardium,[24–26] which are associated with reentrant arrhythmias. In our study, the average interval between onset of myocardial infarction and occurrence of ventricular tachycardia/fibrillation in subgroup 1 was 1 hour. Because these patients also had a high prevalence of ventricular late potentials, this may well support the theory that the mechanism of ventricular tachycardia/fibrillation occurring immediately after acute myocardial infarction in humans is indeed reentry

A limitation of the present study is that signal-averaging was not performed immediately after these hyperacute phase ventricular arrhythmic episodes. However, clinical studies have shown that late potentials can appear as early as 3 hours after onset of myocardial infarction, and presence of late potentials in the subsequent tracings is usually stable.[12,13] We also found a high concordance (unpublished observation) among serial recordings performed during the first 10 days of acute myocardial infarction. Therefore, it seems reasonable to presume that patients in subgroup 1 who had late potentials later on may have had late potentials preceding ventricular tachycardia/fibrillation.

In the experimental laboratory, after "early" ventricular arrhythmias, a relatively quiescent period ensues, followed by "late" ventricular arrhythmias which begin several hours after coronary artery ligation and last up to 48 hours after ligation.[23] There were 9 patients in our study whose ventricular tachycardia/fibrillation developed on the first or second day, and a high prevalence of late potentials was seen in this group (67%; Figure 1). This observation suggests that after early ventricular arrhythmias, reentry may still play a role in causing ventricular tachycardia/fibrillation in the first 2 days of myocardial infarction.

Late potentials and left bundle branch block: In prior published studies, patients with bundle branch block have always been excluded from analysis. In the present study, in patients with left bundle branch block and acute myocardial infarction, signal-averaged electrocardiography differed significantly between those with and without spontaneous hyperacute or acute ventricular arrhythmias. The criteria we used (root-mean-square voltage in the last 40 ms of QRS ≤20 uV) resulted in a 28% prevalence that was similar to a 26% prevalence of late potentials in patients without left bundle branch block. For identifying patients with hyperacute or acute ventricular arrhythmias, this 1 criterion had a 83% sensitivity and 87% specificity. Furthermore, of 29 patients with left bundle branch block, 4 had sudden death during follow-up. Of these 4 patients, 3 had a root-mean-square voltage in the last 40 ms of QRS ≤20 uV. Based on these observations, we suggest that in patients with a left bundle branch block pattern, signal-averaged electrocardiography is a reliable marker to identify those prone to early as well as late ventricular arrhythmias. The sole criterion of root-mean-square voltage ≤20 uV in the last 40 ms of QRS complex seems to be suitable.

Early and late clinical course of patients with ventricular arrhythmias: In the present study, patients with ventricular tachycardia/fibrillation had an unfavorable in-hospital prognosis, including those whose primary ventricular fibrillation occurred within 48 hours of hospital admission. A similar finding has recently been reported by 2 large studies.[16,17] The positive relation found in our study between early in-hospital ventricular arrhythmias and significantly higher creatine kinase and its MB level, as well as significantly lower left ventricular ejection fraction, supports the view that a large-sized infarct and consequent pump failure is often the underlying milieu for recurrent lethal ventricular arrhythmias.

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Importance of Myocardial Infarct Artery Patency on the Prevalence of Ventricular Arrhythmia and Late Potentials After Thrombolysis in Acute Myocardial Infarction

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Sustained infarct artery patency is an important determinant of survival in patients with acute myocardial infarction. We studied 61 patients with acute myocardial infarction who received intravenous recombinant tissue-type plasminogen activator, aspirin or heparin within 6 hours of symptom onset, to determine if infarct artery patency after intravenous thrombolytic therapy influences myocardial electrical stability as measured by the prevalence of spontaneous ventricular ectopy or late potential activity. Infarct artery patency was determined by angiographic evaluation 2.5 ± 3 days after infarction. Forty-eight patients (79%) had a patent infarct-related artery and 13 (21%) patients had an occluded vessel. The mean number of ventricular premature complexes (VPCs)/hour ($p < 0.01$) and the prevalence of late potentials (54 vs 19%; $p < 0.03$) were significantly higher in patients with an occluded versus patent-infarct related vessel. Although VPC frequency and late potentials were not influenced by the time to thrombolytic treatment, patients with a patent infarct-related artery had a lower prevalence of late potentials regardless of whether treatment was initiated ≤2 hours (25% patent vs 50% occluded; p = not significant) or 2 to 6 hours (16% patent vs 55% occluded; $p > 0.03$) after symptom onset.

Thus, successful thrombolysis decreases the frequency of ventricular ectopic activity and late potentials in the early postinfarction phase. The reduction in both markers of electrical instability may help explain why the prognosis after successful thrombolysis is improved after acute myocardial infarction.

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The benefit of thrombolytic therapy on both short- and long-term survival after acute myocardial infarction is well established.[1,2] The mechanisms responsible for enhanced survival in patients treated with thrombolytic therapy remain controversial, but may be related to properties other than preservation of left ventricular function alone.[3] Recent studies have determined that early recanalization and sustained patency of the infarct-related vessel may enhance survival in patients after myocardial infarction by contributing to improved ventricular remodeling and healing, establishing collateral blood flow to noninfarct myocardial segments and reducing electrical instability.[3] The latter mechanism is particularly important since sudden death secondary to malignant ventricular arrhythmia may account for up to 40% of total mortality in the first year after the index infarction.[4,5]

In the present study, we tested the hypothesis that patients with acute myocardial infarction treated within 6 hours of symptom onset with thrombolytic therapy who attain infarct artery patency have a more stable myocardial electrical substrate and reduced prevalence of ventricular arrhythmia and late potential activity in the early postinfarct phase. In addition, the relation between the time from symptom onset to initiation of thrombolytic therapy and infarct artery patency was examined to determine their impact on myocardial electrical stability.

METHODS

Patients: Data were obtained through a retrospective review of 61 patients who presented with ≥30 minutes of chest pain, ST-segment elevation ≥1 mm in ≥2 contiguous leads and who received treatment within 6

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hours of symptom onset with 100 or 150 mg of intravenous recombinant tissue-type plasminogen activator. Patients enrolled in either the Heparin Aspirin Reperfusion Trial[6] or the Thrombolysis In Myocardial Infarction-2B trial from St. Louis and George Washington Universities who underwent all of the following procedures were considered eligible for study entry: (1) a predischarge 24-hour ambulatory and signal-averaged electrocardiogram, and (b) a predischarge diagnostic cardiac catheterization. Patients with an intraventricular conduction delay (QRS duration $\geq$0.11 ms), complete bundle branch block or those taking antiarrhythmic drugs before hospital discharge were excluded.

Cardiac catheterization: Cardiac catheterization was performed 2.5 ± 3 days (mean ± standard deviation) after infarction. Significant coronary artery disease was considered present if a narrowing of $\geq$60% of a major epicardial vessel was observed. Stenosis was determined by digital calipers in orthogonal views or by 2 independent experienced observers. Infarct artery patency was defined by the coronary flow scoring system established in the Thrombolysis in Myocardial Infarction trial.[7] For the purposes of this study, flow grades of 0 to 1 were considered an "occluded" vessel and flow grades of 2 to 3 were considered a "patent" vessel.

Left ventricular ejection fraction was calculated from the 30° right anterior oblique ventriculogram using a standard area-length method. Regional wall motion was subjectively classified as normal, hypokinetic, akinetic or dyskinetic.

Ambulatory electrocardiographic evaluation: Standard 2-channel 24 hour clinical ambulatory electrocardiograms were obtained at a mean of 8 ± 4 days after infarction. The mean number of ventricular premature complexes (VPCs) per hour, ventricular couplets and episodes of ventricular tachycardia ($\geq$3 consecutive VPCs) were assessed.

Frequent ventricular ectopic activity was defined as a mean VPC count of $\geq$10 beats/hour. Complex ventricular ectopy was defined as the presence of either frequent ventricular ectopic activity or ventricular tachycardia, or both. All ambulatory electrocardiographic data were interpreted by physicians unaware of the angiographic findings.

Signal-averaged electrocardiography: Signal-averaged electrocardiograms were recorded using Arrhythmia Research Technology (Austin, Texas) and Corazonix Corporation (Oklahoma City, Oklahoma) recorders a mean of 7 ± 3 days after infarction. Orthogonal X, Y and Z leads were recorded with rejection of ectopic or noisy beats by template recognition. At least 150 beats were amplified and averaged in each recording with noise levels <1.0 mV. After signal-averaging, the data were filtered using a bidirectional digital filter with a bandpass frequency of 40 to 250 Hz. The filtered signals from the 3 leads were combined into a vector magnitude, $\sqrt{x^2 + y^2 + z^2}$, for analysis. Three parameters from the signal-averaged electrocardiogram were examined (Figure 1). The total duration of the filtered QRS (QRS duration) using computer-

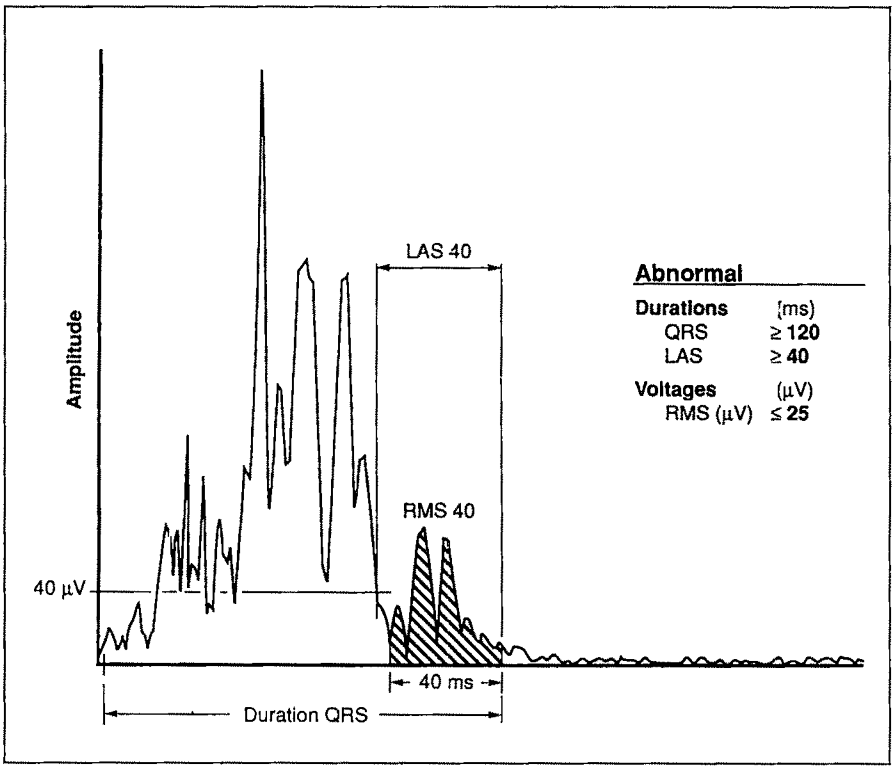

FIGURE 1. Measurement of signal-averaged electrocardiographic parameters. The QRS duration is measured using computer-selected end points, and was considered abnormal if $\geq$120 ms. The low-amplitude signals <40 µV (LAS 40) is measured from the point where the terminal QRS falls below 40 µV to the end of the QRS, and was considered abnormal if $\geq$40 ms. The root-mean-square (RMS 40) of the last 40 ms is demonstrated in the *hatched area* and was considered abnormal if $\leq$25 µV.

TABLE I Patient Characteristics According to Status of Infarct-Related Artery

	Infarct-Related Artery		
Variable	Patent (n = 48)	Occluded (n = 13)	p Value
Age (years)	55 ± 12	58 ± 9	0.47
Men/women	38/10	9/4	0.70
White/black	44/4	11/2	0.82
Prior myocardial infarction (%)	2 (4)	1 (8)	0.84
Congestive heart failure (%)	10 (21)	4 (31)	0.70
Infarct site (%)			0.08
Anterior	27 (56)	3 (23)	
Inferior	20 (42)	10 (77)	
Lateral	1 (2)	0 (0)	
Symptom onset–thrombolytic therapy (hours)	3 ± 1	3 ± 1	0.93

TABLE II Cardiac Catheterization Findings in Patients with Patent and Occluded Infarct Arteries

	Infarct-Related Artery		
	Patent (n = 48)	Occluded (n = 13)	
Variable	n (%)	n (%)	p Value
Time after MI to catheterization (days)	2.6 ± 2.6	2.3 ± 3.2	0.73
Coronary angiography			
No. of coronary arteries ≥ 60% in diameter			0.48
None	4 (8)	0 (0)	
One	25 (52)	5 (42)	
Two	11 (22)	5 (42)	
Three	8 (17)	3 (16)	
% Residual stenosis (mean)	68 ± 21	99 ± 0.3	0.0001
Infarct-related artery			
Right coronary artery	19 (37)	10 (77)	
Left anterior descending artery	27 (56)	3 (23)	0.054
Left circumflex artery	2 (4)	0 (0)	
Left ventriculography			
LV ejection fraction (%)	51 ± 13	46 ± 18	0.32
Segmental wall motion			
Normal	2 (4)	0 (0)	0.86
Hypokinetic	15 (32)	4 (31)	
Akinetic	25 (53)	8 (62)	
Aneurysm	5 (10)	1 (8)	

LV = left ventricular; MI = myocardial infarction.

selected end points was considered abnormal when the duration was $\geq$120 ms. The duration of low-amplitude signals was measured from the point where the terminal QRS decreased to <40 mV to the end of the QRS, and was considered abnormal when the duration was $\geq$40 ms. The root-mean-square was considered abnormal when the value was $\leq$25 mV. Late potential activity was considered present when $\geq$2 of these parameters were abnormal.

Statistical methods: Statistical analysis was performed using the student's *t* test for continuous variables, chi-square with Yates correction for categorical data and Wilcoxon signed-rank test for analysis of nonparametric parameters, where appropriate. Logistic regression analysis was performed with positive late potentials as the dependent variable and 5 clinical and angiographic variables: (1) Left ventricular ejection fraction, (2) size of infarction, (3) degree of residual coronary artery stenosis, (4) segmental wall motion analysis, and (5) infarct artery patency, were used as the independent variables. Data were expressed as mean ± 1 standard deviation. A $p < 0.05$ was considered significant. The effect of the timing of thrombolytic therapy as it relates to the prevalence of VPCs and abnormalities on signal-averaged electrocardiography was evaluated by stratifying the patient population by early ($\leq$2 hours) and late (2 to 6 hours) presentation.

RESULTS

Study group: The final study group consisted of 61 patients (mean age 56 ± 12 years [range 25 to 74]) of whom 77% were men. Mean time from symptom onset to initiation of intravenous thrombolytic therapy was 3.0 ± 1.8 hours (range 0.4 to 6.0). The site of infarction was anterior in 30 patients (49%), inferior in 30 patients (49%) and lateral in 1 patient (2%). Three patients (5%) had a history of a prior myocardial infarction.

Patent versus occluded infarct-related artery: At angiography, 48 (79%) patients had a patent infarct-related artery and 13 (21%) patients had an occluded vessel. There was no difference in baseline characteristics between the 2 groups (Table I).

Cardiac catheterization variables (Table II): The 2 groups had similar cardiac catheterization characteristics. The occluded infarct vessel more often involved the right coronary artery (77%), whereas the left anterior descending artery was the culprit vessel in 56% of patients with a patent infarct-related artery ($p < 0.05$).

Ambulatory and signal-averaged electrocardiographic parameters (Table III): The mean number of VPCs per hour was significantly greater in patients with an occluded versus patent infarct-related artery. However, there was no difference in the prevalence of frequent or complex ventricular ectopic activity between the 2 groups.

Patients with occluded arteries had significantly more abnormal signal-averaged electrocardiographic parameters compared with those with a patent vessel. Of the 13 patients with an occluded infarct artery, 7 (54%) had late potentials present compared with only 9 of 48 (19%) patients with a patent infarct artery (<0.03, Figure 2).

TABLE III Ambulatory and Signal-Averaged Electrocardiographic Variables in Patients with Occluded and Patent Infarct Arteries

	Infarct-Related Artery		
	Patent (n = 48)	Occluded (n = 13)	
Variable	n (%)	n (%)	p Value
Ambulatory ECG			
Time from MI to ambulatory ECG (days)	7 ± 3	8 ± 4	0.57
Recording time (hours)	21 ± 3	22 ± 2	0.28
Ventricular premature complexes (mean/hour)	23 ± 75	106 ± 212	0.01
% Frequent ventricular beats (≥ 10/hour)	10 (20)	4 (33)	0.58
Couplets	15 (31)	3 (25)	0.96
Ventricular tachycardia	9 (18)	1 (8)	0.76
Complex ventricular ectopic activity	12 (26)	4 (33)	0.39
Signal-averaged ECG			
Time of MI to recording (days)	7 ± 3	8 ± 2	0.54
QRS duration (ms)	101 ± 18	105 ± 19	
Low-amplitude signal <40 (ms)	32 ± 11	37 ± 24	0.24
Root-mean-square voltage <40 (mV)	37 ± 26	31 ± 31	0.44
Number of abnormal parameters	0.7 ± 1	1.2 ± 1	0.05
None	28 (58)	5 (38)	
One	11 (23)	1 (8)	
Two	6 (13)	6 (46)	
Three	3 (6)	1 (8)	

ECG = electrocardiogram; MI = myocardial infarction.

Relation of late potentials to arterial patency (Table IV): By univariate analysis only the presence of an occluded infarct-related vessel predicted late potential activity (p = 0.028).

Five clinical and angiographic variables, including regional and global left ventricular function, extent of coronary artery disease, site of infarction and infarct artery patency were entered into a stepwise logistic regression model. Failure to establish infarct artery patency was found to be the only significant predictor of late potentials (β coefficient = 3.052; p <0.005).

Relation of late potentials to time of treatment (Table V): Of the 61 patients, 18 (29%) received early (≤2 hours) intravenous thrombolytic therapy (mean time 1.5 ± 0.5), and 43 (71%) received treatment between 2 and 6 hours (mean time 3.5 ± 1.1) after symptom onset. There was a nonsignificant trend toward greater infarct artery patency, lower prevalence of infarct zone dyskinesia, and a lower prevalence of mean VPCs per hour in patients who were treated within 2 hours. However, there was no difference in the signal-averaged electrocardiographic variables between the 2 groups. Five (28%) patients treated early and 11 (26%) patients treated later had late potentials present (p = not significant).

TABLE IV Clinical and Angiographic Predictors of Late Potential Activity

	Late Potentials		
	Present (n = 16)	Absent (n = 45)	
	n (%)	n (%)	p Value
Clinical parameters			
Time from MI to signal-averaged ECG (days)	8 ± 4	7 ± 3	0.19
Symptom onset—thrombolytic therapy (hours)	3 ± 2	3 ± 1	0.49
Peak creatine kinase (U/liter)	2,495 ± 2,036	2,382 ± 1,721	0.83
Prior MI	1 (6)	2 (4)	0.70
Congestive heart failure	4 (25)	10 (22)	0.91
Medications	(n = 15)	(n = 45)	
β blockers	6 (40)	21 (49)	0.60
Digoxin	2 (13)	3 (7)	0.85
ACE inhibitor	4 (27)	5 (11)	0.23
Angiographic parameters	(n = 16)	(n = 45)	
Time of MI to catheterization (days)	3 ± 4	2 ± 2	0.20
No. of coronary arteries ≥60% ↓ in diameter (%)			
Zero	0 (0)	4 (8)	0.22
One	7 (44)	23 (52)	
Two	4 (25)	13 (28)	
Three	5 (31)	5 (11)	
Infarct-related artery			
Left anterior descending	8 (50)	22 (49)	0.72
Right coronary	7 (44)	22 (49)	
Circumflex	1 (6)	1 (2)	
Occluded infarct artery	7 (44)	6 (13)	0.028
% Mean residual stenosis	84 ± 21	71 ± 23	0.06
LV ejection fraction (%)	45 ± 14	52 ± 14	0.11
>55%	4 (27)	17 (39)	0.60
35–55%	7 (46)	22 (49)	0.94
<35%	4 (27)	5 (11)	0.31
Regional wall motion	12 (73)	28 (62)	0.67
akinetic/diskinetic			0.76
TIMI flow grade			
Zero	6 (38)	5 (11)	
One	1 (6)	1 (2)	
Two	1 (6)	8 (18)	
Three	8 (50)	31 (69)	

ACE = angiotensin-converting enzyme; TIMI = Thrombolysis in Myocardial Infarction trial; ↓ = decrease; other abbreviations as in Tables II and III.

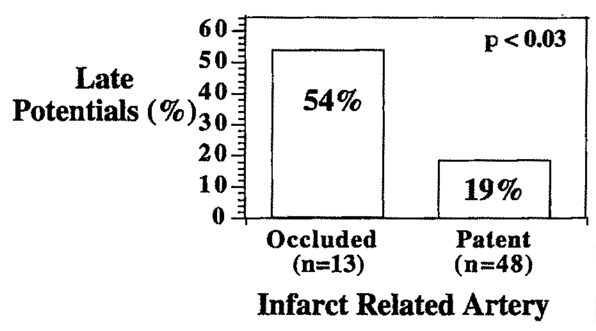

FIGURE 2. The frequency of late potentials was significantly greater in patients with an occluded versus patent infarct-related vessel (p<0.03).

TABLE V Comparison of Early (≤2 hours) Versus Late (>2 hours) Initiation of Thrombolytic Therapy on Catheterization, Ambulatory and Signal-Averaged Electrocardiographic Parameters

Variable	Symptom Onset to Initiation of Therapy: ≤2 Hours (n = 18) n (%)		>2 Hours (n = 43) n (%)		p Value
Mean time to thrombolytic therapy (hours)	2 ± 1		4 ± 1		—
Cardiac catheterization					
Infarct artery patency	16 (89)		32 (74)		0.36
Left ventricular ejection fraction (%)	48 ± 16		50 ± 14		0.20
≤35%	2 (11)		7 (16)		0.94
Dyskinetic infarct zone	1 (6)		5 (12)		0.80
Ambulatory electrocardiography					
Ventricular premature complexes (mean/hour)	4 ± 6		64 ± 153		0.06
% Frequent ventricular beats (>10/hour)	22		26		0.86
Complex ventricular beats (%)	28		26		0.96
Signal-averaged electrocardiography					
QRS duration (ms)	101 ± 18		102 ± 19		0.87
Low-amplitude signal <40 ms	30 ± 14		35 ± 15		0.26
Root-mean-square voltage <40 mV	39 ± 26		35 ± 27		0.58
Late potential present	5 (28)		11 (26)		0.89
	Occluded (n = 2)	Patent (n = 16)	Occluded (n = 11)	Patent (n = 32)	
Late potentials based (%)	1 (50)	4 (25)	6 (55)	5 (16)*	

*p <0.03.

Patients with a patent infarct vessel had a lower prevalence of late potentials whether treated ≤2 or >2 hours after symptom onset (Table V). Of the 43 patients treated 2 to 6 hours after symptom onset, 11 had an occluded infarct-related vessel, 6 (55%) of whom had late potentials present. In contrast, of the 32 patients who had a patent infarct artery, only 5 (16%) had late potentials (p <0.03). A similar but nonsignificant trend was also noted in patients with a patent infarct artery who were treated earlier (≤2 hours).

DISCUSSION

Enhanced survival associated with intravenous thrombolytic therapy for acute myocardial infarction has been demonstrated, and has mainly been attributed to preservation of left ventricular function.[1,2] However, the mechanisms of improved survival appear to be multifactorial, and may result from improved infarct artery patency and electrical stability.[3,8,9] The results of this study support the concept that infarct artery patency after successful thrombolysis may enhance electrical stability as reflected by a reduction of both the prevalence of VPCs and late potentials in patients with acute myocardial infarction.

Relation of infarct artery patency to myocardial electrical stability: Frequent and complex ventricular ectopy have been recognized as significant and independent adverse prognostic factors in patients after myocardial infarction.[4,5,10,11] However, the influence of thrombolysis on ventricular ectopy after infarction remains poorly defined.

Theroux et al[12] retrospectively analyzed the ambulatory electrocardiographic data recordings in patients after infarction treated with either intravenous streptokinase or conventional therapy. Patients receiving thrombolytic therapy had a significantly lower prevalence of ventricular ectopic activity than those treated conventionally. Similar findings were reported by Turito et al,[13] who also demonstrated a significantly lower prevalence of both VPCs (3.2 vs 6.4 VPCs/hour; p <0.05) and complex ventricular arrhythmia (p <0.01) in patients with a patent versus occluded infarct-related vessel. In the present study, infarct artery patency was also associated with a reduction in spontaneous ventricular ectopy, but only demonstrated a trend toward decreased complex ventricular ectopy (Table III).

Late potential activity is also associated with an adverse prognosis when detected in the recovery phase of acute myocardial infarction.[14-16] Recent evidence suggests that thrombolytic therapy may enhance electrical stability and reduce the prevalence of late potentials in the postinfarct period.[17-19] In the study by Gang et al,[17] signal-averaged electrocardiography performed within 48 hours of infarction revealed a significantly lower prevalence of late potentials in patients receiving recombinant tissue-type plasminogen activator than in those receiving conventional therapy (5 vs 23%; p <0.01). Importantly, late potentials were present in only 14% compared with 33% of patients with a patent vs occluded infarct-related artery. Similar data have been reported by Vatterott et al[18] and Zimmerman et al.[19]

Although other investigators have not confirmed these findings,[13,20] the use of different thrombolytic agents, differences in the timing of cardiac catheterization and the criteria used to define an abnormal signal-averaged electrocardiogram have been postulated as factors explaining these divergent results. Nonetheless, these data collectively indicate a lower prevalence of late potentials in patients following successful thrombolysis.

Potential mechanisms relating infarct artery patency to electrical stability in acute myocardial infarction: Recent experimental and clinical studies have shown that early reperfusion may improve infarct healing by altering myocardial cellular hemorrhage and edema formation, and by enhancing washout of toxic metabolites.[21,22] In addition, successful thrombolysis has been associated with improved left ventricular remodeling[23] and a decrease in left ventricular expansion and aneurysm formation.[24,25] These factors appear to lead to a more homogenous cellular infarct zone and may partially explain the resultant stability in the myocardial electrical substrate after successful thrombolytic reperfusion.[26]

Ventricular ectopic activity, late potentials and time from symptom onset to treatment: The greatest mortality reduction after thrombolytic therapy is noted in those presenting within the first hour of symptom onset.[2] In the current study, early treatment did not result in a lower prevalence of ventricular ectopy or late potentials. However, infarct artery patency was an important determinant of late potential activity regardless of the timing of thrombolytic therapy (Table V). Although our data represent a small patient subset, the findings suggest an important role of infarct artery patency in stabilizing the myocardial electrophysiologic substrate even when fibrinolytic therapy is not initiated early after symptom onset.

Study limitations: Coronary angiography (2.5 ± 3 days) and ambulatory signal-averaged electrocardiographic (mean 8 ± 4 days) evaluations were not obtained at similar times. Although coronary reocclusion may have occurred between the time of angiography and noninvasive testing, the impact in the present study is expected to be small, since reocclusion after successful thrombolysis usually occurs early (24 to 48 hours) after initiation of therapy.[27] The greater frequency of late potentials in patients with an occluded infarct artery may be related to the site of infarction (e.g., inferior location) in this group. Previous studies indicate that the signal-averaged electrocardiogram is abnormal in a higher proportion of patients with inferior than anterior myocardial infarction.[14,15] This may be due to a later depolarization of the inferoposterior segment of the left ventricle. However, in this study, infarct location was not a predictor of late potentials by multivariant analysis.

Because of the relatively small study size the favorable trends in VPC reduction noted between groups precludes definite conclusions regarding prognostic importance. Also, the criteria for defining abnormal signal-averaged electrocardiographic parameters are not firmly established.[28] The criteria used in the current study are based on known prognostic findings in patients with sustained ventricular tachycardia at our institution.[29]

Conclusion: Thus, improved survival after successful thrombolytic reperfusion may be attributable, at least in part, to a more favorable arrhythmic risk profile in the recovery phase of acute myocardial infarction.

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Usefulness of QRST Time-Integral Values of 12-Lead Electrocardiograms in Diagnosing Healed Myocardial Infarction Complicated by Left Bundle Branch Block

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The usefulness of QRST time-integral (I_{QRST}) values of 12-lead electrocardiograms for diagnosing a prior myocardial infarction complicated by left bundle branch block (LBBB) was determined. The study consisted of 25 patients with LBBB (11 with and 14 without myocardial infarction). The I_{QRST} values in each lead point of 12-lead electrocardiograms were calculated. Data from 607 normal subjects were used as controls and mean ± 2 standard deviations was regarded as the normal range. The following parameters were derived: number of leads less than the normal range of I_{QRST} values (nQRST) and sum of the differences between the normal mean I_{QRST} value and I_{QRST} value of a given patient in leads where this value was less than the normal range (ΣQRST). The criteria of nQRST (12-lead) ≥ 5 and ΣQRST (12-lead) ≥ 500 μV in 12-lead electrocardiograms were selected on a relative cumulative frequency distribution and demonstrated the presence of a myocardial infarction in LBBB with a sensitivity of 82% and a specificity of 100% for each. With regard to the localization of the myocardial infarction, the criterion of ΣQRST (V_{1-6}) ≥ 300 μV in leads V_{1-6} of 12-lead electrocardiograms demonstrated the presence of an anterior myocardial infarction in the LBBB with a sensitivity of 88% and a specificity of 77%. It was difficult to localize an inferior myocardial infarction in patients with LBBB by using I_{QRST} values of inferior leads. This study demonstrates the practical usefulness of I_{QRST} values in 12-lead electrocardiograms for diagnosing prior myocardial infarction in the presence of LBBB.

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A 12-lead electrocardiographic diagnosis of myocardial infarction complicated by left bundle branch block (LBBB) is difficult.[1-4] Whereas various criteria have been proposed[5-9] for improving the diagnostic ability of myocardial infarction complicated by LBBB, they are not yet satisfactory.[10-12] Recently, we reported that QRST isointegral maps were useful in detecting a myocardial infarction complicated by BBB.[13] However, there have been no reports concerning the clinical usefulness of QRST time-integral (I_{QRST}) values of 12-lead electrocardiograms in diagnosing a myocardial infarction complicated by BBB. The latest electrocardiographic recorders equipped with analog/digital converters make it easier to calculate I_{QRST} values accurately from 12-lead electrocardiograms. The purpose of this study was (1) to investigate whether I_{QRST} values in 12-lead electrocardiograms could be useful for diagnosing a prior myocardial infarction complicated by LBBB, (2) to compare the diagnostic ability of I_{QRST} values with that of previously reported criteria for diagnosing a prior myocardial infarction complicated by LBBB, and (3) to determine whether I_{QRST} values could localize a prior myocardial infarction complicated by LBBB.

METHODS

Patients: Patients who had complete LBBB in 12-lead electrocardiograms[14] and who visited our hospital were included in the present study if (1) a complete medical history was obtained, and (2) there were no obvious underlying heart diseases except for myocardial infarction assessed by routine examinations including echocardiography and Doppler echocardiography. In all, 25 patients had LBBB. Fourteen (9 men and 5 women; mean age 66 years) were free from obvious underlying heart diseases ($LBBB_N$ group). A myocardial infarction was ruled out by echocardiographic findings such as wall motion, thickness and systolic thickening, thallium-201 (Tl-201) scintigraphy and coronary arteriography when necessary. The remaining 11 patients with LBBB (9 men and 2 women; mean age 68

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TABLE I Normal Mean I_{QRST} Values in Six Groups

	Older-Aged Group (≥70 years)		Middle-Aged Group (40 years to 70 years)		Younger-Aged Group (<40 years)	
Leads	Men (n = 32)	Women (n = 35)	Men (n = 126)	Women (n = 102)	Men (n = 218)	Women (n = 94)
I	41 ± 14	37 ± 25	49 ± 19	44 ± 20	43 ± 22	35 ± 19
II	60 ± 23	56 ± 22	72 ± 25	61 ± 23	82 ± 31	62 ± 24
III	19 ± 25	19 ± 21	23 ± 28	16 ± 24	39 ± 31	26 ± 20
aVR	−50 ± 14	−47 ± 20	−61 ± 18	−52 ± 18	−63 ± 22	−49 ± 19
aVL	11 ± 17	9 ± 21	13 ± 21	14 ± 19	2 ± 22	5 ± 15
aVF	39 ± 23	37 ± 17	48 ± 25	39 ± 22	61 ± 29	44 ± 20
V_1	7 ± 28	−11 ± 15	2 ± 27	−12 ± 18	0 ± 29	−16 ± 18
V_2	72 ± 41	33 ± 27	81 ± 48	38 ± 31	59 ± 63	15 ± 37
V_3	117 ± 46	80 ± 28	129 ± 49	82 ± 37	101 ± 72	66 ± 46
V_4	119 ± 41	90 ± 27	133 ± 47	92 ± 33	126 ± 60	79 ± 46
V_5	98 ± 30	85 ± 25	109 ± 37	85 ± 29	104 ± 42	74 ± 18
V_6	67 ± 23	62 ± 17	73 ± 25	62 ± 21	72 ± 28	57 ± 23

Values are mean ± standard deviation (μV).
I_{QRST} = QRST time integral.

years) had a history of myocardial infarction ($LBBB_{MI}$ group). A diagnosis of myocardial infarction was obtained by a history of prolonged chest pain accompanied by ST-T changes and elevation of creatine phosphokinase, and the location of the myocardial infarction was confirmed by either a transmural perfusion defect on Tl-201 myocardial scintigraphy or wall motion abnormalities on left ventriculography. The time at which the myocardial infarction occurred ranged from 1 month to 8 years (mean 3 years) before the study in $LBBB_{MI}$ group. The location of the myocardial infarction was anterior in 8 and inferior in 3 patients in the $LBBB_{MI}$ group.

QRST time-integral values of 12-lead electrocardiograms: I_{QRST} values in each lead point of 12-lead electrocardiograms were calculated from the multiplexed data recorded simultaneously by an HPM-6500 (Chunichi Denshi, Japan) with a sampling interval of 1 ms. Because the precise method to calculate I_{QRST} values has been reported elsewhere,[15,16] we will describe it only briefly. We processed the calculation of I_{QRST} value as follows (1) One QRST complex was selected from recorded data. (2) Two-point baseline adjustment by choosing the flat portion of the TP segment before the P and after the T deflection was performed. (3) Time instants of QRS onset and T offset were determined manually using lead II of the magnified electrocardiogram. (4) I_{QRST} value for each lead as the algebraic sum of all potentials from the QRS onset to T offset multiplied by the sampling interval was calculated. The normal mean I_{QRST} values were derived from data obtained from 607 normal subjects registered in the Japanese Circulation Society Task Force Committee on Criteria for Body Surface Mapping,[17] who were free from cardiovascular diseases by routine clinical examination including 12-lead electrocardiograms. Normal persons were divided into 6 groups according to age and gender. The normal I_{QRST} values in each group are listed in Table I.

When the I_{QRST} value in each lead point was less than the normal mean − 2 standard deviations of the corresponding normal group, the reduction was considered statistically significant. The following parameters were then derived: number of leads less than the normal range of I_{QRST} values (nQRST); and sum of the differences between the normal mean I_{QRST} value and I_{QRST} value of a given patient in leads where this value was less than the normal range (ΣQRST). To diagnose the presence of myocardial infarction in patients with LBBB, we calculated the nQRST (12-lead) and ΣQRST (12-lead) in 12-lead electrocardiograms. To diagnose the localization of the myocardial infarction in patients with LBBB, we subsequently calculated the nQRST (V_{1-6}), ΣQRST (V_{1-6}), nQRST (II, III and aVF) and ΣQRST (II, III and aVF) in leads V_{1-6} or II, III and aVF of 12-lead electrocardiograms.

The 12-lead electrocardiograms of all patients were examined to determine if they satisfied the previously proposed criteria, such as Cabrera's sign,[6] for the diagnosis of a myocardial infarction in the presence of LBBB by 2 cardiologists unaware of the subjects' clinical data.

Statistical analysis: Sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy were determined for each test criterion and expressed as a percentage. Data were expressed as mean ± standard error of the mean. A relative cumulative frequency distribution was used to determine the diagnostic criteria for detecting complicated myocardial infarction by the parameters, nQRST and ΣQRST. To compare the difference of mean values of nQRST or ΣQRST between groups, analysis by Student's *t* test was performed. The null hypothesis was rejected when the p value was <0.05.

RESULTS

Diagnosis of myocardial infarction in patients with left bundle branch block: LEFT BUNDLE BRANCH BLOCK COMPLICATED BY MYOCARDIAL INFARCTION: I_{QRST} values and 12-lead electrocardiograms of a representative case of LBBB complicated by myocardial infarction are shown in Figure 1. In this case there was a perfusion defect of the Tl-201 scintigram in the anteroseptal wall. The patient was 65 years old and the I_{QRST} values in leads II, aVF and V_{2-5} were below the normal range corresponding the middle-aged male group. The nQRST (12-lead) was 6, and ΣQRST (12-lead) 667 μV in this case.

LEFT BUNDLE BRANCH BLOCK UNCOMPLICATED BY MYOCARDIAL INFARCTION: I_{QRST} values and 12-lead electrocardiograms of a representative case of LBBB uncomplicated by myocardial infarction are shown in Figure 2. The Tl-201 scintigram revealed no perfusion defect. The patient was 72 years old and the nQRST (12-lead) was 0; ΣQRST (12-lead) was 0 μV in this case, corresponding the older-aged male group.

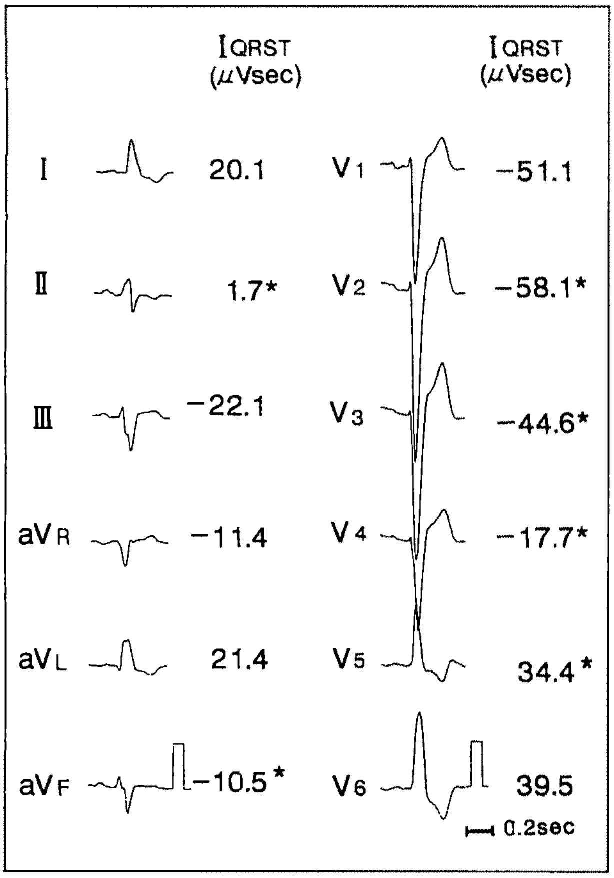

FIGURE 1. QRST time-integral (I_{QRST}) values and 12-lead electrocardiograms of a representative patient with left bundle branch block complicated by an anterior myocardial infarction. I_{QRST} value in leads II, aVF and V_{2-5} were less than the normal range (*). The number of leads less than the normal range of I_{QRST} values {(nQRST) (12-lead)} was 6, the sum of the differences between the normal mean I_{QRST} value and I_{QRST} value of a given patient in lead where this value was less than the normal range {(ΣQRST) (12-lead)} was 667 μV, nQRST (V_{1-6}) was 4, and ΣQRST (V_{1-6}) was 539 μV.

DIAGNOSTIC ABILITY FOR DIAGNOSING MYOCARDIAL INFARCTION COMPLICATED BY LEFT BUNDLE BRANCH BLOCK: Figure 3 shows that the nQRST (12-lead) and ΣQRST (12-lead) were significantly greater in the LBBB$_{MI}$ group (5.7 ± 0.7, 641 ± 76 μV) than in the LBBB$_{N}$ group (2.1 ± 0.4, 167 ± 30 μV) ($p < 0.001$). The criterion of nQRST (12-lead) ≥5 was selected on the statistical basis for detecting myocardial infarction. The diagnostic ability on this criterion showed a sensitivity of 82%, a specificity of 100% and a diagnostic accuracy of 92%. With regard to ΣQRST (12-lead), the criterion of ΣQRST (12-lead) ≥500 μV was selected on the statistical basis. With use of this criterion, the diagnostic ability was not improved (Table II).

Localization of myocardial infarction in patients with left bundle branch block: Because we obtained a considerably high diagnostic ability in diagnosing a myocardial infarction with I_{QRST} values, we examined whether the I_{QRST} values of 12-lead electrocardiograms could diagnose not only the presence but also the site of a myocardial infarction in the presence of LBBB.

ANTERIOR MYOCARDIAL INFARCTION: nQRST (V_{1-6}) showed no significant difference between patients with LBBB with (3.6 ± 0.5) and without (2.4 ± 0.4) an

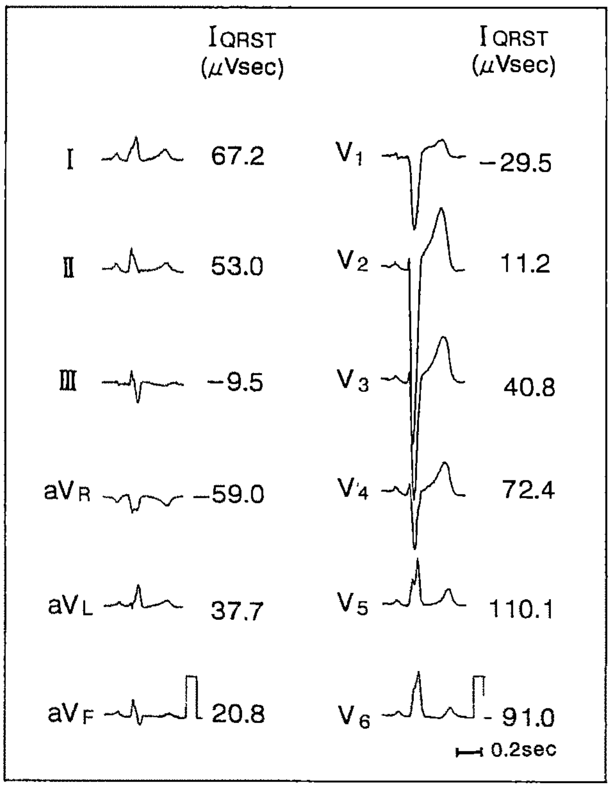

FIGURE 2. I_{QRST} and 12-lead electrocardiograms of a representative patient with left bundle branch block uncomplicated by a myocardial infarction. The nQRST (12-lead) was 0, and ΣQRST (12-lead) was 0 μV. Abbreviations as in Figure 1.

TABLE II Diagnostic Ability of nQRST (12-lead) and ΣQRST (12-lead) in Identifying Myocardial Infarction Complicated by Left Bundle Branch Block

	nQRST (12-lead) ≥5	ΣQRST (12-lead) ≥500 μV
Sensitivity (%)	82	82
Specificity (%)	100	100
Predictive value (+) (%)	100	100
Predictive value (−) (%)	88	88
Diagnostic accuracy (%)	92	92

Predictive value (+) = predictive value of a positive test; Predictive value (−) = predictive value of a negative test.
See text for explanation of nQRST and ΣQRST.

anterior myocardial infarction. However, ΣQRST (V_{1-6}) was significantly greater in patients with LBBB with (506 ± 93 μV) than without (230 ± 49 μV) anterior myocardial infarction ($p < 0.01$) (Figure 4). The criterion of ΣQRST (V_{1-6}) ≥300 μV was selected on the statistical basis for detecting an anterior myocardial infarction. The diagnostic ability of the criteria showed a sensitivity of 88%, a specificity of 77%, and a diagnostic accuracy of 80% (Table III).

INFERIOR MYOCARDIAL INFARCTION: nQRST (II, III and aVF) and ΣQRST (II, III and aVF) showed no significant difference between patients with LBBB with (1.3 ± 0.3, 78 ± 32 μV) and without (0.7 ± 0.2, 46 ± 16 μV) inferior myocardial infarction, respectively (Figure 5).

DIAGNOSTIC ABILITY OF OTHER ELECTROCARDIOGRAPHIC CRITERIA FOR DIAGNOSING MYOCARDIAL INFARCTION COMPLICATED BY LEFT BUNDLE BRANCH BLOCK (TABLE IV): The following 5 signs previously proposed in published reports were examined in our series; (1) initial notching of the R wave in leads I, aVL and V_6 (Chapman and Pearce[5]); (2) notching 0.04 second in duration in the ascending limb of the S wave of leads V_{3-5} (Cabrera and Friedland[6]); (3) notching of the first 0.04 second of the QRS complex in leads II, III and aVF (notching)[1]; (4) Q wave >0.03 second in duration in leads I, aVL and V_5 or V_6[5,7–9]; (5) Q wave >0.03 second in duration in leads II, III and aVF.[3,8] The diagnostic ability of the 5 signs were calculated and are listed in Table IV. The sensitivity of all signs for diagnosing a myocardial infarction tended to be low and were variable, ranging from 9 to 46%.

DISCUSSION

In this study we showed that the localized abnormalities due to a prior myocardial infarction can be detected in the presence of LBBB by I_{QRST} values of 12-lead electrocardiograms. It has been reported that 12-lead electrocardiographic diagnosis of a myocardial infarction complicated by BBB, especially LBBB, is difficult.[1–4] Various electrocardiographic criteria have been proposed to improve the diagnostic ability of myocardial infarction in the presence of LBBB (Table IV).[5–9] In the present study, the sensitivity of I_{QRST} values in 12-lead electrocardiograms for identifying myocardial infarction complicated by LBBB was superior to the previously reported criteria including Cabrera's sign and the Q wave in leads I, aVL, V_5 or V_6 (82 vs <46%).

There have been many reports concerning the usefulness of body surface mapping in diagnosing myocardial infarction undetectable by 12-lead electrocardiograms.[18,19] Hirai et al[20] experimentally showed the pos-

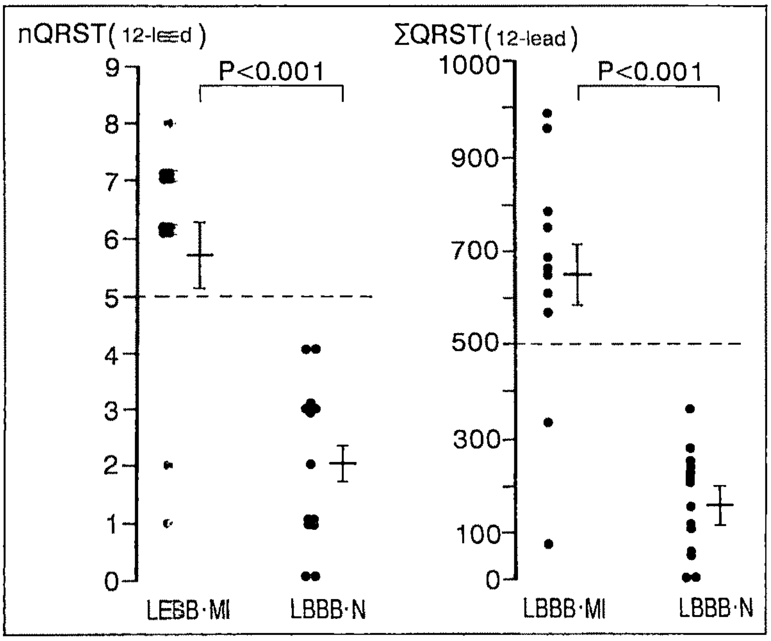

FIGURE 3. Plots of nQRST (12-lead) *(left panel)* and ΣQRST (12-lead) *(right panel)* in patients with LBBB who had a history of myocardial infarction ($LBBB_{MI}$ group) (n = 11) and patients with LBBB who were free from underlying heart diseases ($LBBB_N$ group) (n = 14) groups. The nQRST (12-lead) and ΣQRST (12-lead) were significantly greater in the $LBBB_{MI}$ than the $LBBB_N$ group ($p < 0.001$). The criteria of nQRST (12-lead) ≥5 *(dashed line in left panel)* and ΣQRST (12-lead) ≥500 μV *(dashed line in right panel)* were selected on the statistical basis for diagnosing a myocardial infarction complicated by LBBB. *Bars* represent mean ± standard error of the mean. Other abbreviations as in Figure 1.

sibility of using PQRST isointegral maps for detecting a myocardial infarction in the presence of LBBB. QRST isointegral maps were introduced by Abildskov et al[21,22] and are based on the concept of ventricular gradient.[23] It has been reported that the ventricular gradient,[23] the vector of time-integral of the QRST loop, is largely independent of activation sequence and dependent on recovery properties. Recently, we demonstrated that QRST isointegral maps are highly useful in diagnosing myocardial infarction complicated by BBB.[13] The rationale for using QRST isointegral maps

TABLE III Diagnostic Ability of ΣQRST (V_{1-6}) in Identifying Anterior Myocardial Infarction Complicated by Left Bundle Branch Block

	ΣQRST (V_{1-6}) $\geq$300 μV
Sensitivity (%)	88
Specificity (%)	77
Predictive value (+) (%)	64
Predictive value (−) (%)	93
Diagnostic accuracy (%)	80

Abbreviations as in Table II.

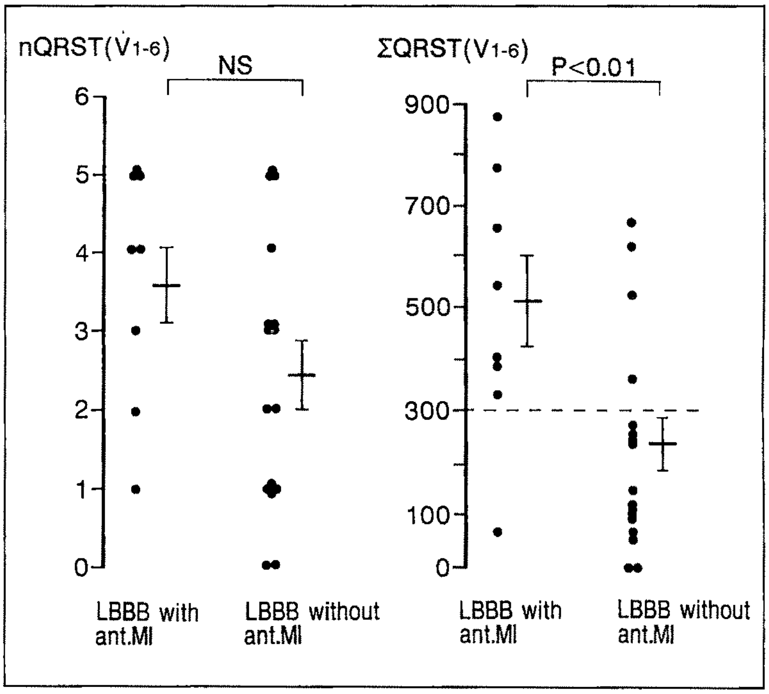

FIGURE 4. Plots of nQRST (V_{1-6}) *(left panel)* and ΣQRST (V_{1-6}) *(right panel)* in the LBBB group with ($n = 8$) and without an anterior myocardial infarction ($n = 17$). The nQRST (V_{1-6}) was not significantly different (NS) between patients with and without an anterior myocardial infarction. However, the ΣQRST (V_{1-6}) was significantly greater in the LBBB group with than without an anterior myocardial infarction ($p < 0.01$). The criterion of ΣQRST (V_{1-6}) $\geq$300 μV *(dashed line in right panel)* was selected on the statistical basis for diagnosing an anterior myocardial infarction complicated by LBBB. *Bars* represent mean ± standard error of the mean. Other abbreviations as in Figure 1.

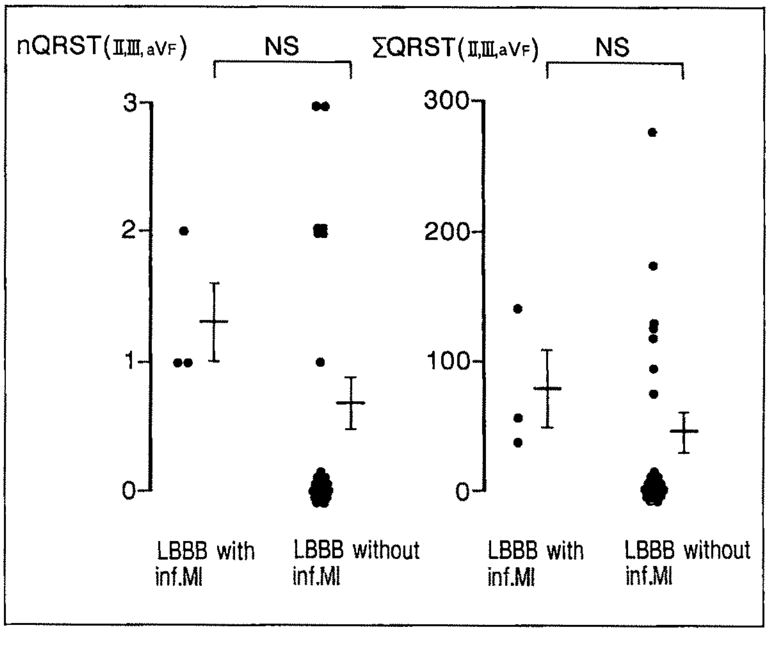

FIGURE 5. Plots of nQRST (II, III and aVF) *(left panel)* and ΣQRST (II, III and aVF) *(right panel)* in the LBBB group with ($n = 3$) and without an inferior myocardial infarction ($n = 22$). The nQRST (II, III and aVF) and ΣQRST (II, III and aVF) in the LBBB group did not differ significantly (NS) between the 2 groups. *Bars* represent mean ± standard error of the mean. Abbreviations as in Figure 1.

TABLE IV Diagnostic Ability of Previously Reported Criteria in Identifying Myocardial Infarction Complicated by Left Bundle Branch Block (n = 25

			12-Lead ECG Criteria						
			Chapman[5]	Cabrera[6]†	Notching[1]‡	Q-1,L,V_6[5,7–9]	Q-2,3,F[3,8]	ΣQRST (12-lead) ≧500 μV	ΣQRST (V_{1-6}) ≧300 μV
SN	(%)	All MI	46	36	36	46	9	82	
		Ant. MI	50	38	38	63	0	75	88
		Inf. MI	33	33	33	0	33	100	
SP	(%)		43	86	64	93	93	100	77
PV (+)	(%)		39	67	44	83	50	100	64
PV (−)	(%)		50	63	56	68	57	88	93
DA	(%)		44	64	52	72	56	92	80

Chapman = initial notching of the R wave in leads I, aVL and V_6.

†Cabrera = notching 0.04 second in duration in the ascending limb of the S wave of leads V_{3-5}.

‡Notching = notching of the first 0.04 second of the QRS complex in leads II, III and aVF.

Ant. = anterior; DA = diagnostic accuracy; ECG = electrocardiographic; Inf. = inferior; MI = myocardial infarction; PV (+) = predictive value of a positive test; PV (−) = predictive value of a negative test; Q-1,L,V_6 = Q wave > 0.03 second in duration in leads I, aVL, V_5 or V_6; Q-2,3,F = Q wave > 0.03 second in duration in leads II, III and aVF; SN = sensitivity; SP = specificity.

for diagnosing myocardial infarction with an abnormal activation sequence is that the localized abnormalities of recovery properties due to myocardial infarction should be manifest in QRST isointegral maps independent of activation sequence. In this study, we applied the same rationale to I_{QRST} values of 12-lead electrocardiograms, the advantages of which are easier, more simple and practical compared with body surface maps.

The diagnostic ability of I_{QRST} values in this study was superior to the previously proposed criteria. The sensitivity, specificity and diagnostic accuracy provided by the criterion of ΣQRST (12-lead) for detecting a myocardial infarction complicated by LBBB using I_{QRST} values were 82, 100 and 92%, whereas the diagnostic ability of the previous criteria for detecting a myocardial infarction were poor in this study. Although we observed a high diagnostic ability for detecting the presence of myocardial infarction with I_{QRST} values, it was difficult to localize an inferior myocardial infarction. There are several reasons for the difficulty in diagnosing an inferior myocardial infarction using I_{QRST} values. First, a voltage of an electrocardiogram in the inferior leads is relatively low. Second, even normal subjects have Q waves and negative T waves in the inferior leads.[24] These factors may decrease I_{QRST} values in the inferior leads. In addition, in some patients with an inferior myocardial infarction, a diagnostic Q wave in any inferior lead cannot be seen.[25] However, some patients with an inferior myocardial infarction showed abnormally low I_{QRST} values in precordial leads and thus satisfied the criteria for the presence of myocardial infarction. Coexisting myocardial ischemia or fibrosis of the anterior wall in addition to an inferior myocardial infarction[26] may produce abnormally low I_{QRST} values, because patients with BBB occasionally have an advanced coronary heart disease[27] and often are elderly.

Study limitations: First, the diverse conditions associated with LBBB suggest that a nonspecific pathologic process may also be common to most etiologic factors. We could not definitely rule out the possibility that patients with LBBB without myocardial infarction were in a pathologic process due primarily to aging. Such a condition would mimic an infarction, resulting in the I_{QRST} values lower than the normal mean − 2 standard deviations. Second, because this study group was rather small, further study with larger patient populations are needed to confirm the validity of the findings.

Clinical implications: This study demonstrates the practical usefulness of I_{QRST} values of 12-lead electrocardiograms in diagnosing myocardial infarction complicated by LBBB. Although QRST isointegral maps have shown a high diagnostic ability to diagnose myocardial infarction complicated by LBBB,[13] the method is cumbersome. The I_{QRST} values of 12-lead electrocardiograms, as proposed in this study, are practical and have better diagnostic ability than the criteria previously proposed. I_{QRST} values of 12-lead electrocardiograms, which will be obtained more easily and accurately by the latest electrocardiographic recorders equipped with A/D converters, may provide new information on electrocardiographic diagnosis.

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Effects of High-Density Lipoprotein on Acetylcholine-Induced Coronary Vasoreactivity

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David Y. Lu, MD, and Charles E. Rackley, MD

Recent evidence suggests that high-density lipoprotein (HDL) cholesterol has important vasoactive properties which may contribute to its beneficial effects on atherosclerotic coronary artery disease. The endothelium-dependent vasodilator acetylcholine has been used in a number of experimental studies to assess endothelial function. The relation between serum lipoproteins and acetylcholine-induced coronary vasoreactivity was investigated in patients (n = 27) undergoing elective coronary arteriography. Mean serum cholesterol, low-density lipoprotein cholesterol, HDL cholesterol and triglyceride levels were 189 ± 7 (4.84 ± 0.18 mmol/liter), 134 ± 6 (3.47 ± 0.15 mmol/liter), 41 ± 3 (1.06 ± 0.08 mmol/liter) and 106 ± 30 mg/dl (1.20 ± 0.03 mmol/liter), respectively. After a baseline arteriogram, acetylcholine was infused into the left main coronary artery and percent change from baseline dimension was determined in 27 angiographically smooth coronary artery segments and in 14 arterial segments with evidence of mild atherosclerotic disease. Intact vascular smooth muscle function was then confirmed in all segments by dilation to intracoronary nitroglycerin. Acetylcholine produced significant vasoconstriction of both angiographically smooth (13 ± 4%, $p < 0.05$ vs baseline) and diseased (19 ± 4%, $p < 0.05$ vs baseline) coronary segments. A positive correlation was observed between HDL cholesterol and normal acetylcholine-induced coronary vasoreactivity in both angiographically smooth ($r = 0.59$, $p < 0.001$) and diseased ($r = 0.62$, $p < 0.02$) coronary segments. No significant correlation was observed, however, between total and low-density lipoprotein cholesterol, or between total cholesterol to HDL ratio and the response of coronary artery diameter to acetylcholine infusion. These findings suggest that HDL cholesterol promotes normal endothelial cell function in both normal and atherosclerotic coronary segments. This beneficial effect may be related to a direct effect of HDL on release of endothelial-derived relaxing factor or may be secondary to its effects on endothelial cell proliferation. Thus, while HDL has important antiatherogenic properties, the clinical benefit of HDL elevation may be related, in part, to its effects on endothelial function and coronary vasoreactivity.

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Epidemiologic data[1] have established a link between low levels of high-density lipoprotein (HDL) and the incidence of atherosclerotic coronary events, whereas pharmacologic elevation of HDL was associated with a reduction in the incidence of fatal and nonfatal myocardial infarctions in the Helsinki Heart Study.[2] The beneficial effect of HDL has been attributed to its role in reverse cholesterol transport; however, recent data suggest that HDL has other beneficial vascular properties including antithrombotic,[3] and prostacyclin-stabilizing activity.[4–6] In addition, HDL has been shown to significantly enhance vascular endothelial cell proliferation.[7] Recently, a relation has been established between elevated serum cholesterol and abnormal vasoconstrictor response to the endothelium-dependent vasodilator, acetylcholine.[8–11] Previous in vitro studies[12,13] on the effect of HDL on coronary vasoreactivity have yielded conflicting results. We sought to determine the relation between HDL cholesterol and coronary endothelial function by examining the correlation between serum lipoproteins and effect of acetylcholine on angiographically determined coronary artery diameter in humans.

METHODS

Patient selection: The study protocol was approved by the Georgetown University Investigational Review Board. Informed consent was obtained from patients who had been scheduled to undergo their first elective cardiac catheterization for evaluation of possible coronary artery disease. To minimize the risks of acetylcholine-induced coronary occlusion or heart block, subjects were excluded if hemodynamically significant coronary

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artery disease (>50% diameter reduction of a major epicardial coronary artery) or a left dominant coronary circulation were noted at the time of catheterization. Twenty-seven patients met these criteria and constitute the study group.

Study protocol: All vasoactive medications were withheld ≥24 hours before cardiac catheterization. After an overnight fast, coronary arteriography was performed using standard angiographic catheters. Heparin (3,000 U) was administered intravenously; however, nitroglycerin or other vasoactive agents were not administered during catheterization. A baseline angiogram of the left coronary artery was then recorded using 6 to 8 ml ionic contrast (Berlex, Wayne, New Jersey) power-injected (Med-Rad, Pittsburgh, Pennsylvania) at a rate of 5 to 6 ml/s. After completion of the baseline angiogram, acetylcholine was infused according to the method of Werns et al.[14] Briefly, a 0.2 mM solution of acetylcholine was infused at 0.8 ml/min for 3 minutes into the coronary ostium through the angiographic catheter using an infusion pump (Harvard Instruments, S. Natick, Massachusetts). At the completion of the infusion, a post-acetylcholine angiogram was then recorded in the same projection using the same rate and volume of contrast material. A second dose of acetylcholine (1.6 ml/min) was then infused followed by a third angiogram. A final angiogram was then performed after the intracoronary administration of nitroglycerin (200 μg). Angiograms were primarily recorded in a cranial right anterior oblique projection and tightly collimated to image only the proximal and mid-left anterior descending or circumflex coronary artery. The position of the image tube remained constant throughout each study in order to minimize magnification errors. Pincushion distortion was minimized by keeping the arterial segment of interest within the central third of the image field and panning was not performed in order to minimize motion artefact.

Angiographic analysis: Angiographic analysis was performed using a previously validated computer-assisted edge-detection system[15] (ADAC Laboratories, San Diego, California). In our laboratory this system has been found to have high degree of reproducibility with low interobserver ($r = 0.98$, standard error of the estimate = 0.09) and intraobserver ($r = 0.98$, standard error of the estimate = 0.09) variability. Analysis was performed by an investigator who was unaware of both the intervention and the lipid profile results. An angiographically smooth segment of the left anterior descending or circumflex coronary artery, which was free of any overlapping or branch vessels, was identified in each subject. Segment diameter was determined at baseline after both acetylcholine infusions and nitroglycerin administration. Images were calibrated using the measured diameter of the catheter, and absolute vessel diameter was determined as the average of 3 measurements. The higher dose of acetylcholine always produced a greater degree of vasoconstriction or vasodilation in each individual subject. Therefore, the effect of the maximal dose of acetylcholine on segment diameter was expressed as percent change from baseline for each subject. A total of 14 segments with angiographic evidence of coronary artery disease were observed within the sections of coronary arteries imaged in this study. These segments contained primarily mild luminal irregularities or stenosis that did not exceed 25% diameter reduction. The response to acetylcholine in each diseased segment was determined at the site of minimal luminal diameter and expressed as a percent change from baseline.

Serum lipid analysis: Fasting venous blood was obtained before heparinization from the femoral sheath at the time of catheterization. Total cholesterol and triglycerides were determined by fluorescence spectroscopy using a commercially available reagent system and analyzer (Abbott Laboratories, Chicago, Illinois). HDL was determined using similar methods after precipitation of low-density lipoprotein (LDL) and very low density lipoprotein with high molecular weight dextran. LDL was then calculated according to the Friedewald formula.[16]

Statistical analysis: Data are presented as mean ± standard error of the mean. Student's *t* test was used to evaluate the effect of acetylcholine on systemic hemodynamics and coronary artery diameter. Correlations between vasoreactivity and lipid levels were performed using linear regression analysis. Comparisons were considered statistically significant at $p < 0.05$.

RESULTS

Patient characteristics: The study population consisted of 20 men and 7 women (mean age 53 ± 2 years [range 34 to 70]). Angiography was performed to evaluate atypical chest pain in 14, chest pain consistent with angina in 7, and an abnormal exercise test in 4 asymptomatic subjects. One patient underwent coronary arteriography for unexplained dyspnea and 1 for evaluation of mitral regurgitation. Lipid profile results and response of individual patients to acetylcholine are listed in Table I.

Systemic hemodynamics: Acetylcholine infusion had no effect on systemic hemodynamics. Heart rate before and after acetylcholine infusion was 72 ± 3 and 72 ± 4 beats/min (p = not significant), respectively, whereas mean aortic pressure was 94 ± 4 mm Hg at baseline and 92 ± 3 mm Hg (p = not significant) after acetylcholine infusion.

Effect of acetylcholine on coronary artery diameter: Acetylcholine significantly reduced the diameter of angiographically smooth coronary segments 13 ± 4% (p

TABLE I Lipids and Response to Acetylcholine

Pt. No.	Age (yr) & Sex	Risk Factors				Lipids (mg/dl)					ACH Response	
		SH	CS	DM	FH	TC	LDL	HDL	Trig.	TC/HDL	Smooth	CAD
1	70 M	+	+	0	+	163	96	63	18	1.5	16.0	—
2	46 F	+	0	0	0	130	102	47	77	2.8	13.8	—
3	66 M	+	+	0	0	200	153	39	42	5.1	12.0	—
4	61 F	+	0	0	0	219	124	75	100	2.9	8.5	2.0
5	61 F	0	0	0	0	188	139	44	27	3.2	8.0	—
6	69 M	+	0	0	0	207	146	55	33	2.7	0.0	—
7	40 M	+	+	0	0	166	110	49	34	2.3	−1.5	—
8	56 M	+	+	0	0	242	200	40	13	5.1	−2.6	−8.6
9	35 M	0	+	0	0	210	155	42	68	3.7	−4.0	—
10	70 F	+	0	0	0	142	95	38	44	3.7	−5.3	−19.4
11	51 M	+	+	+	0	222	156	26	198	8.7	−5.9	−47.0
12	48 F	+	0	0	0	195	139	41	71	4.7	−8.3	−25.3
13	40 F	+	+	+	0	192	138	46	39	3.0	−9.6	—
14	48 M	+	0	0	+	196	152	33	56	6.0	−10.0	−4.5
15	55 F	0	0	0	+	148	95	51	15	1.9	−10.4	—
16	66 M	+	0	0	+	189	128	50	58	3.8	−11.8	−18.3
17	68 M	+	+	0	+	135	100	33	13	3.0	−17.6	—
18	55 M	+	+	0	0	241	192	27	109	8.9	−18.1	−39.5
19	69 M	+	0	+	0	201	146	45	50	4.5	−18.2	−25.0
20	34 M	+	0	+	+	296	187	35	372	8.4	−23.2	−7.6
21	53 M	0	+	0	+	180	112	34	112	5.3	−25.0	−23.1
22	44 M	0	0	0	+	191	141	44	29	3.2	−27.5	1.2
23	60 M	0	+	0	0	180	139	35	32	4.0	−31.0	—
24	51 M	+	+	+	0	178	103	43	159	2.4	−32.0	−23.6
25	48 M	0	+	0	+	137	97	24	170	5.7	−34.0	−32.0
26	44 M	0	+	+	0	204	166	28	51	6.0	−48.1	—
27	34 M	0	0	0	0	176	113	30	166	3.8	−66.0	—
Mean	53 ± 2					189 ± 7	134 ± 6	41 ± 3	106 ± 30	3.9 ± 0.4	−13.0 ± 3.7	−19.3 ± 3.9

ACH Response = % change in diameter after acetylcholine (maximal dose): CAD = segments with coronary disease; CS = cigarette smoker; DM = diabetes mellitus; FH = family history of coronary disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SEM = standard error of the mean; SH = systemic hypertension; Smooth = smooth arterial segments; TC = total cholesterol; Trig. = triglycerides; + = vasodilation; − = vasoconstriction.

<0.05 vs baseline) and diseased segments 19 ± 4% (p <0.05) from baseline values (Figure 1). All segments dilated (smooth 18 ± 3%, diseased 12 ± 4%) after the administration of intracoronary nitroglycerin confirming intact smooth muscle vasodilatory capacity. No correlation was observed between response to acetylcholine and nitroglycerin in individual segments, suggesting that the response of segments to acetylcholine was due to its endothelium-dependent actions and not related to a nonspecific effect on smooth muscle.

Serum lipids and coronary vasoreactivity: A significant positive correlation (r = 0.59, p <0.001) was observed between HDL cholesterol and the effect of acetylcholine on the diameter of angiographically smooth coronary segments (Figure 2). Subjects with a normal vasodilatory response to acetylcholine had significantly (p <0.001) higher HDL values (54 ± 6 mg/dl, 1.40 ± 0.04 mmol/liter) than those with an abnormal vasoconstrictive response (38 ± 2 mg/dl, 0.99 ± 0.05 mmol/liter). A positive correlation (r = 0.62, p <0.02) was

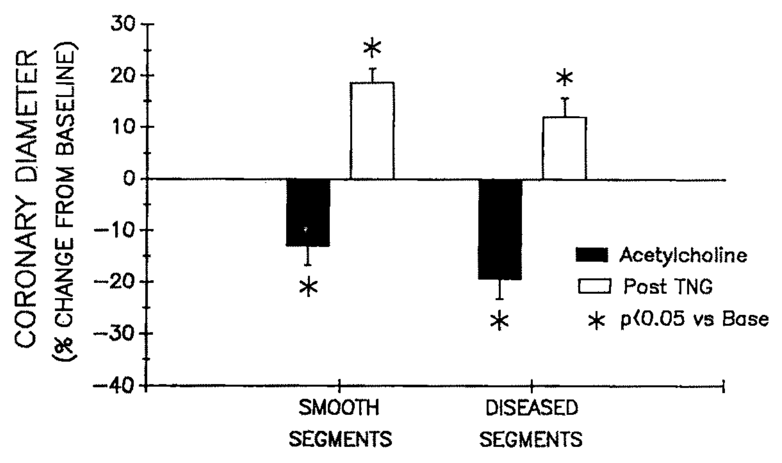

FIGURE 1. Effect of intracoronary acetylcholine *(solid bars)* and nitroglycerin (TNG) *(open bars)* on coronary artery diameter in angiographically smooth segments and segments with evidence of coronary artery disease. Base = baseline value.

also observed between HDL cholesterol and the effect of acetylcholine on the diameter of diseased coronary segments (Figure 3). However, no significant relation was observed between acetylcholine-induced vasoreactivity and total or LDL cholesterol in either smooth or diseased segments. An inverse correlation between total to HDL cholesterol ratio and diameter response to acetylcholine was observed in smooth (r = −0.33, p = 0.09) and diseased (r = −0.46, p = 0.10) segments; however, these correlations did not achieve statistical significance. No correlation was observed between other cardiovascular risk factors and response to acetylcholine (Table I).

DISCUSSION

A link has been established between low HDL and the incidence of atherosclerotic coronary events. In the Helsinki Heart Study,[2] a significant reduction in fatal and nonfatal myocardial infarction was observed after administration of gemfibrozil, and increased HDL was identified as the single most important predictor of a favorable outcome. The beneficial effect of HDL is often attributed to its role in reverse cholesterol transport. Recent data suggest that HDL has other properties that may contribute to its salutary effects on coronary artery disease. Saku et al[3] demonstrated that HDL has antithrombotic properties. Recently, apolipoprotein A-1, the major apolipoprotein component of HDL, has been identified as prostacyclin stabilizing factor[4] and reductions in prostacylcin half-life associated with unstable angina and myocardial infarction can be corrected with HDL supplementation.[6] In addition, HDL has been shown to enhance endothelial cell proliferation.[7]

Prior in vitro studies examining the vasoactive effects of HDL have yielded conflicting results.[12,13] The present study is the first to investigate the relation between HDL, endothelial function, and in vivo human coronary artery vasoreactivity. A significant correlation was observed between HDL cholesterol and normal response of coronary arteries to the endothelium-dependent vasodilator acetylcholine in both angiographically normal and mildly diseased coronary artery segments. This finding suggests that HDL cholesterol contributes in some manner to endothelial cell integrity and release of endothelial-derived relaxing factor. This conclusion is consistent with the observations of Tauber et al[7] who demonstrated that HDL cholesterol is a major promoter of endothelial cell proliferation and repair. Thus, the beneficial effects of HDL on coronary vasoreactivity observed in the present study may be related to the enhanced number of functioning endothelial cells from which endothelial-derived relaxing factor can be re-

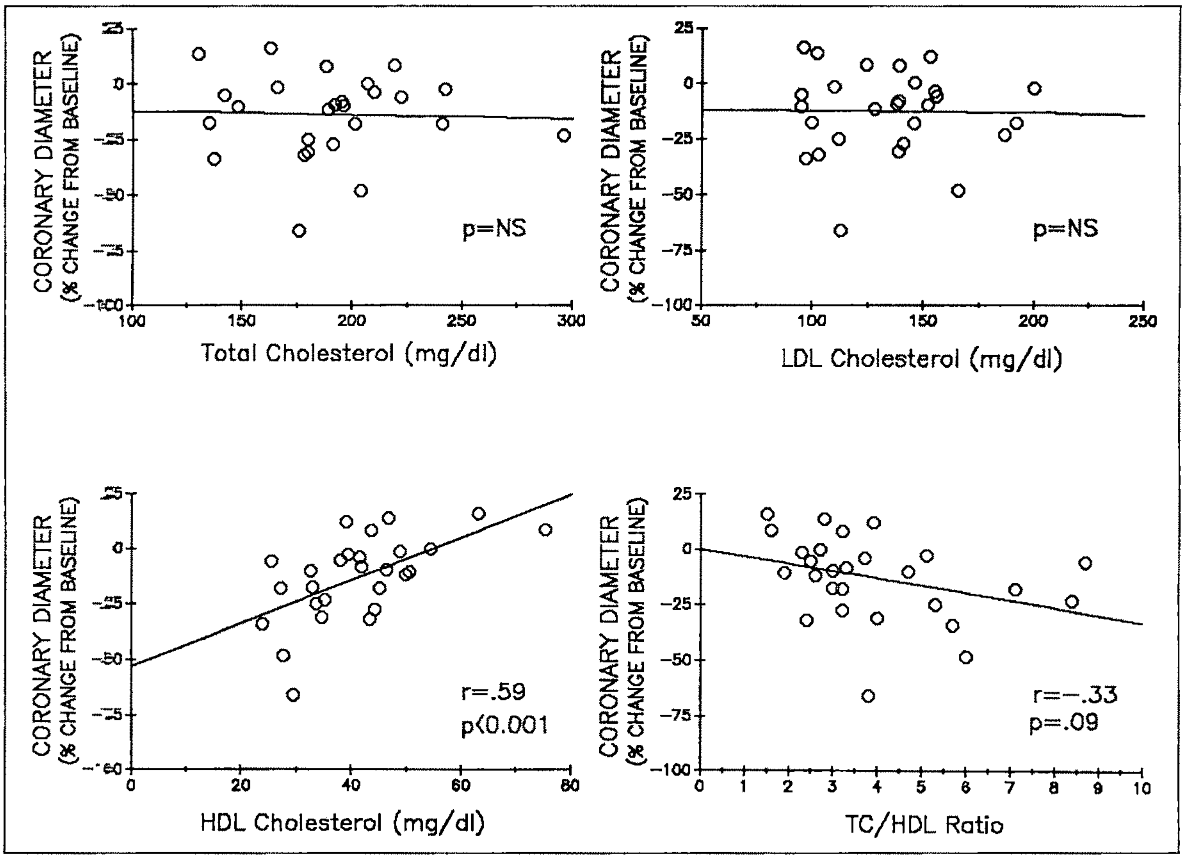

FIGURE 2. Relation between serum lipids and response of coronary artery diameter to acetylcholine infusion in angiographically smooth coronary segments. HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant; TC = total cholesterol.

leased. HDL-induced increases in prostacyclin production and half-life[4-6] may also contribute to its beneficial effects on coronary vasoreactivity.

Several animal studies[11,17,18] have suggested that elevated cholesterol impairs endothelial function and vasoreactivity. However, these studies used atherogenic diets that induced extremely elevated cholesterol levels. In separate human studies, Vita[8] and Zeiher[9] and their co-workers observed impaired coronary response to acetylcholine in hypercholesterolemic patients with angiographically normal coronary arteries. These investigators did not, however, examine the relation between HDL, LDL and coronary vasoreactivity in their study populations. In the present study, no significant correlation was observed between total cholesterol and coronary vasoreactivity in either normal-appearing or mildly diseased coronary segments. This discrepancy may be related to differences in study populations as the subjects in the present study were older and had relatively normal total serum cholesterol levels compared with those studied by Vita and Zeiher and their colleagues. In addition, the present investigation included subjects with mild coronary artery disease, and it is possible that the effects of total cholesterol on vasoreactivity of coronary arteries is diminished with aging, especially as atherosclerosis begins to develop. Thus, in older patients with early coronary artery disease, HDL may have a stronger influence on endothelial integrity than levels of total cholesterol. Indeed, data from the Framingham study suggests that HDL, and not total cholesterol, is the most important predictor of coronary artery disease risk in subjects aged >50 years.[19]

The association between LDL cholesterol and coronary vasoreactivity remains controversial. Although some investigators[20,21] have concluded that LDL inhibits endothelium-dependent vasodilation in vitro, others[22] have not observed this effect. Recent data[23] suggest that oxidative modification of LDL is required for its atherogenic effects and oxidized LDL has been found to inhibit endothelium-dependent vasoreactivity in isolated rabbit aortic strips.[21] Whereas the oxidative modification of LDL has been shown to occur in vitro, the evidence for in vivo generation of oxidized LDL remains indirect.[23] The present study is the first to investigate the effect of LDL cholesterol on in vivo human coronary vasoreactivity. No significant relation was observed between LDL cholesterol and acetylcholine-induced coronary vasoreactivity in either angiographically normal or atherosclerotic coronary artery segments.

Potential study limitations: For safety considerations, we excluded patients with hemodynamically significant coronary artery disease. It is possible that the correlation between HDL and coronary vasoreactivity observed in patients with mild disease may not exist in

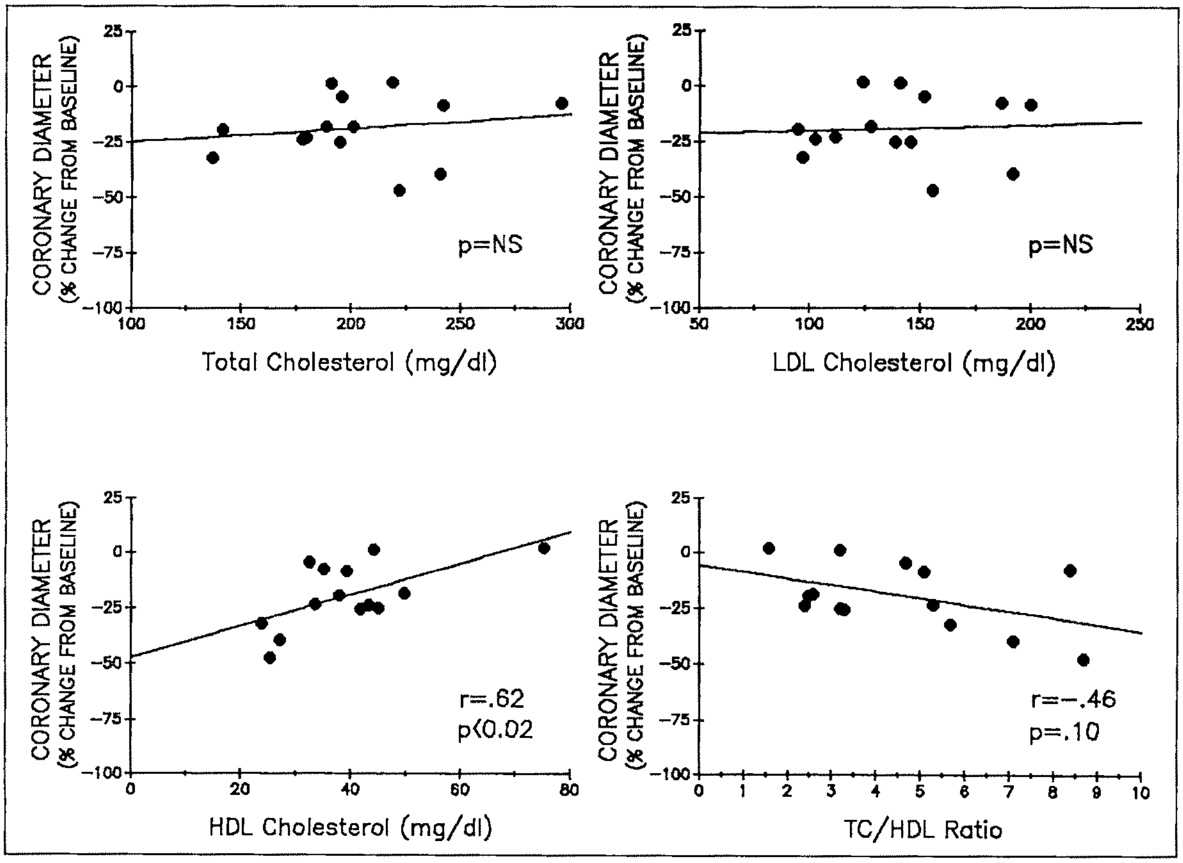

FIGURE 3. Relation between serum lipids and response of coronary artery diameter to acetylcholine infusion in segments with evidence of mild coronary artery disease. Abbreviations as in Figure 2.

patients with more advanced coronary artery disease. In addition, the total and LDL cholesterol levels of the study population were relatively normal. We cannot exclude the possibility that a significant relation between total cholesterol, or LDL cholesterol and coronary vasoreactivity may be observed in subjects with more abnormal lipid profiles.

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Effects of Serum Lipid Levels on Restenosis After Coronary Angioplasty

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Although the association of serum lipid levels with the risk of atherosclerosis is well-recognized, the relation between these levels and restenosis after coronary angioplasty is uncertain. This study examines 186 patients enrolled in a trial of fish oil for prevention of restenosis. Fasting lipid levels (cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides) were measured before angioplasty, and in 90 patients repeated at 6-month follow-up. Fifty-nine patients (32%) developed clinical restenosis confirmed by angiography. Patients who went on to develop restenosis underwent multivessel angioplasty ($p < 0.05$) and were more likely to be on lipid-lowering therapy at baseline (27 vs 13%; $p < 0.05$). In addition, they had higher baseline cholesterol/HDL ratios (6.5 ± 2.2 vs 5.9 ± 2.0; $p < 0.05$) and triglyceride levels (233 ± 210 vs 183 ± 112 mg/dl; $p < 0.05$). Multiple logistic regression analysis confirmed cholesterol/HDL ratios at baseline ($p = 0.021$) and follow-up ($p = 0.0008$) to be independent predictors of risk for restenosis. Using these data, regression lines have been developed that predict risk of restenosis based on type of procedure and on lipid values. These results suggest that serum lipid levels may be associated with the risk of clinical restenosis after coronary angioplasty.

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Although the association of serum lipid levels with risk of atherosclerosis is well established,[1,2] the relation between these levels and the risk of restenosis after coronary angioplasty remains controversial. Some studies have suggested that patients with hypercholesterolemia[3,4] or low levels of high-density lipoprotein (HDL) cholesterol are at increased risk for restenosis. However, other studies have failed to reveal any association between lipid levels and restenosis.[5–7] These studies varied widely in time of assessment of lipid levels, definition of dyslipidemia, patient follow-up, and method used to determine restenosis (clinical versus angiographic). The present study examines the effect of prospectively measured lipids on clinical restenosis in a cohort of patients undergoing coronary angioplasty.

METHODS

Study design: Data from all patients were obtained prospectively as part of a randomized trial of fish oil in patients undergoing angioplasty,[8,9] which revealed no effect of fish oil supplements on restenosis, or total or HDL cholesterol levels. The present study was designed to more closely analyze the influence of lipid levels on restenosis. All aspects of the protocol were approved by the hospital's committee on clinical investigations, and informed consent was obtained from all patients.

Between March 1987 and April 1988, 222 patients scheduled to undergo angioplasty at the Beth Israel Hospital were enrolled in the study. Exclusion criteria included recent significant bleeding, concurrent use of oral anticoagulants, angioplasty of a saphenous vein bypass graft, acute myocardial infarction within 5 days, use of thrombolytic therapy on the same admission, and inability to receive aspirin or to perform a standard treadmill exercise test. Thirty-three patients in this study receiving lipid-lowering therapy at the beginning of the trial were not excluded, but no alteration in this therapy was permitted during the 6-month study period.

Of 222 patients enrolled, 204 underwent angioplasty (11 dropped out or were excluded before angioplasty, and 7 did not undergo angioplasty), of which 186 (93%) were successful. Multivessel angioplasty was performed in 62 patients (33%). All patients were treated with aspirin (325 mg daily), dipyridamole (50 mg 4

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TABLE I Baseline Clinical Characteristics

	Restenosis	No Restenosis	p Value
No. of pts.	59	127	NS
Age (yrs)*	59 ± 10	58 ± 9	NS
Male sex	78%	79%	NS
Unstable angina	32%	38%	NS
Smoking	28%	32%	NS
Fish oil therapy	74%	63%	NS
Lipid-lowering therapy	27%	13%	<0.05
Number of narrowings dilated/pt.*	1.53 ± 0.59	1.31 ± 0.56	<0.05

*Values represent mean ± standard deviation.
NS = not significant.

TABLE II Baseline Lipid Levels

	Restenosis	No Restenosis	p Value
No. of pts.	59	127	
Total cholesterol (mg/dl)	222 ± 43	215 ± 47	NS
HDL cholesterol (mg/dl)	37 ± 10	40 ± 12	NS
Cholesterol/HDL	6.5 ± 2.2	5.9 ± 2.0	<0.05
Triglyceride (mg/dl)	233 ± 210	183 ± 112	<0.05
LDL cholesterol (mg/dl)	145 ± 39	141 ± 45	NS

Values represent mean ± standard deviation.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant.

TABLE III Lipid Levels in 90 Patients with Follow-Up

	Restenosis	No Restenosis	p Value
No. of pts.	35	54	
Baseline			
Total cholesterol (mg/dl)	220 ± 34	213 ± 50	NS
HDL cholesterol (mg/dl)	35 ± 11	42 ± 14	<0.01
Cholesterol/HDL	6.8 ± 2.4	5.4 ± 1.8	<0.005
Follow-up			
Total cholesterol (mg/dl)	216 ± 28	216 ± 47	NS
HDL cholesterol (mg/dl)	36 ± 15	47 ± 14	<0.005
Cholesterol/HDL	6.7 ± 2.4	5.0 ± 1.7	<0.001

Values represent mean ± standard deviation.
Abbreviations as in Table II.

times daily) and calcium antagonists for the duration of the study. Restenosis was identified clinically by the presence of recurrent angina or a newly positive exercise test (≥1 mm ST-segment depression at 80 ms after the J point, or a reversible thallium defect in the area of the myocardium supplied by the dilated vessel not present on the predischarge study, or both), and was confirmed angiographically as the presence of ≥70% stenosis in a previously successfully dilated segment. The investigator performing patient follow-up was unaware of baseline serum lipid levels.

Lipid and lipoprotein analysis: Fasting blood specimens were obtained before initiation of fish oil or placebo therapy in all patients (mean 5.2 ± 3.2 days before angioplasty). In addition, 90 patients had fasting specimens obtained 6 months after angioplasty. Approximately 10 ml of blood were collected in a serum separator tube (Corvac, Sherwood Medical, St. Louis, Missouri) and were centrifuged at 1,000× g. Serum analysis was performed at the clinical chemistry laboratory of Beth Israel Hospital, using a COBAS-BIO centrifugal analyzer (Roche Diagnostic Systems, Nutley, New Jersey). Cholesterol and triglycerides were measured using a standard enzymatic assay (Abbott Laboratories, North Chicago, Illinois); HDL cholesterol was measured simultaneously after treatment with magnesium phosphotungstate (Sigma Diagnostics, St. Louis, Missouri). Typical interassay coefficients of variation for these assays were: cholesterol, 1.1% at 246 mg/dl and 2.1% at 139 mg/dl; HDL cholesterol, 5.8% at 26 mg/dl; and triglycerides, 3.5% at 185 mg/dl and 5.5% at 100 mg/dl. Low-density lipoprotein (LDL) cholesterol was calculated using the formula [total cholesterol − HDL cholesterol − triglyceride/5], when triglyceride was ≤400 mg/dl.

Statistical analysis: Data were prospectively collected and analyzed using the STATA statistical package (Santa Monica, California). All results are presented as mean ± standard deviation. Comparisons between groups with and without restenosis were performed using unpaired Student's *t* test for continuous variables, and the chi-square test for discrete variables. Results were considered significant at $p < 0.05$. Logistic regression analysis was used to test relations between independent variables and restenosis.

RESULTS

Of 186 patients with initially successful angioplasty, 59 (32%) developed clinical restenosis (recurrent angina or positive exercise test, or both) that was confirmed by angiography in 56. The remaining 3 patients classified as positive for restenosis had both angina and a positive exercise test, but refused angiography. Of 127 patients classified as without restenosis, 12 (6%) underwent confirmatory angiography. Of the remaining 115 patients, 104 (90%) were asymptomatic, and 108 (94%) underwent exercise testing that was negative for restenosis. Of 7 patients with neither angiography or exercise testing, 6 were asymptomatic; the remaining patient had an inferior myocardial infarction 3 months after angioplasty of the left anterior descending artery, but no subsequent angina. No patients died or were lost to follow-up.

Baseline clinical characteristics of the groups with and without restenosis are listed in Table I. Patients who eventually developed restenosis were more likely to be on lipid-lowering drugs. In spite of treatment, the 33 patients on lipid-lowering drugs had significantly higher baseline levels of cholesterol, triglycerides, cholesterol/HDL ratio and LDL cholesterol. Baseline lipid levels are listed in Table II. There were significant differences in triglyceride levels and cholesterol/HDL ratio between the groups with and without restenosis.

Lipid levels in the 90 patients with follow-up lipids available are listed in Table III. This group was not randomly selected, but was composed of patients for whom geographic and personal considerations made a return visit feasible. There were no significant differences in restenosis rates (40 vs 32%) or baseline lipid levels between this subset and the entire group. Because of the effect of fish oil on serum triglycerides (mean decrease from baseline to follow-up 30%) and LDL cholesterol (mean increase 8%), only cholesterol and HDL levels, which showed no significant change in the patients treated with fish oil, are shown. In these 90 patients, there were prominent differences in HDL levels and cholesterol/HDL ratios at baseline and follow-up between groups with and without restenosis.

Multiple logistic regression was used to determine the independent correlates of restenosis. For the entire group, the number of lesions dilated ($p = 0.007$) and the baseline cholesterol/HDL ratio ($p = 0.021$) were independent predictors of restenosis. Sex, cigarette smoking, presence of unstable angina, and fish oil therapy versus placebo were not predictors. For the 90 patients available at 6-month follow-up, HDL cholesterol level and cholesterol/HDL ratio at the follow-up measurement correlated with restenosis, and logistic regression determined that the ratio was the single best independent predictor ($p = 0.0008$). Changes in cholesterol, HDL or ratio were not predictive of restenosis.

The actual restenosis rates for patients with various levels of cholesterol/HDL ratio are shown in Figure 1. Using these data, regression lines curves can be developed that predict the probability of restenosis for patients undergoing angioplasty (Figure 2). A patient in the present study with a baseline cholesterol/HDL ratio of 6.0 undergoing 1-lesion angioplasty would have a risk of clinical restenosis of 26%, whereas the same patient undergoing multivessel angioplasty would have a risk of 39%. A patient with a baseline ratio of 4.0 would have risks of 20 and 31%, respectively. Similar estimates can be made for risk of restenosis based on lipid levels during follow-up. The 45 patients with a follow-up cholesterol/HDL ratio >5.5 had a risk of restenosis of 55%, whereas the 45 with a ratio <5.5 had a risk of 24% ($p = 0.003$).

DISCUSSION

A large number of factors predictive of restenosis after angioplasty have been identified.[10] These include factors intrinsic to the patient (male sex, diabetes, cigarette smoking and unstable or variant angina), and related to the lesion location or morphology (proximal left anterior descending artery or vein graft location, total occlusion and bend point) and to the procedure (inadequate result after angioplasty). Studies that have examined the potential role of serum lipids in the restenosis process have been inconclusive.[3-8] Myler et al,[3] in a group of patients undergoing multivessel angioplasty, found that those with cholesterol levels >300 mg/dl were more likely to have restenosis at all sites; a separate study by Austin et al[4] found that hypercholesterol-

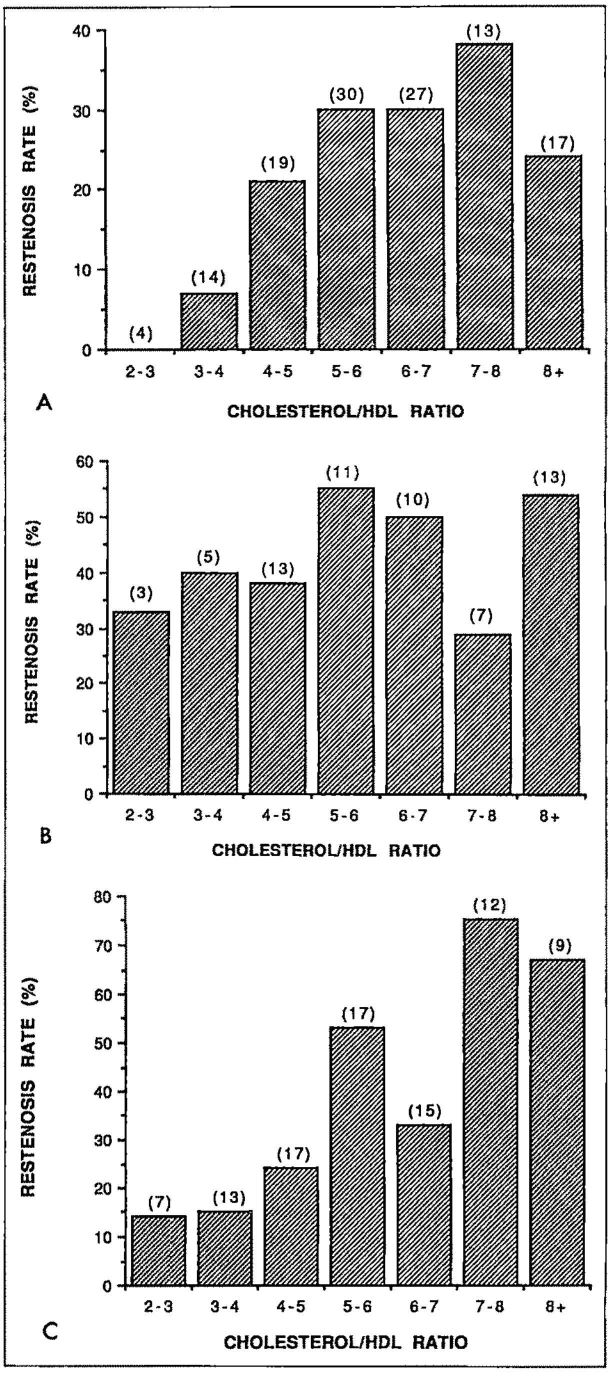

FIGURE 1. Effect of cholesterol/high-density lipoprotein (HDL) ratio on clinical restenosis rates for various groups of patients. *A,* baseline ratio, 1-vessel percutaneous transluminal coronary angioplasty (PTCA); *B,* baseline ratio, multivessel PTCA; *C,* follow-up ratio in 90 patients (1- and multivessel PTCAs combined). Numbers in *parentheses* represent numbers of patients in each subgroup.

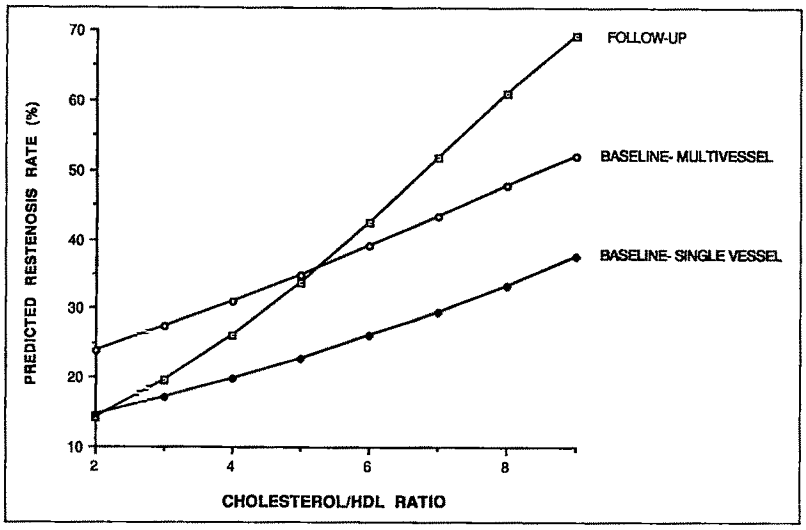

FIGURE 2. Predicted clinical restenosis rates using logistic regression analysis of data shown in Figure 1. For any level of baseline cholesterol/high-density lipoprotein (HDL) ratio, restenosis is more frequent with multivessel angioplasty. Correlation between ratio and restenosis is more prominent at follow-up.

emia was a risk factor in women treated with aspirin. Examinations of other data[5-7] have failed to reveal an association between lipoprotein levels and restenosis, as has a meta-analysis[10] of the published studies. However, most of these studies have been limited by the inability to measure lipid levels and to obtain follow-up data in a prospective cohort of patients; rather, they were analyses of a subset of patients from a database that had lipid and clinical follow-up data available.

In the present study, serum lipid levels, especially cholesterol/HDL ratio, were significant independent predictors of risk of restenosis. Although morphologic studies of restenosis lesions have generally shown intense cellular proliferation without lipid or apolipoprotein accumulation,[11-13] there are potential mechanisms by which lipid metabolism could influence the cellular proliferative process. Balloon angioplasty in a canine renal artery model causes an increase in acyl coenzyme A:cholesterol acyltransferase activity, resulting in increased cholesteryl ester synthesis.[14] It is possible that this increased cholesterol incorporation reflects a need of proliferating cells for cholesterol. Inhibition of cholesterol synthesis with compactin in vitro prevents cellular proliferation in response to platelet-derived growth factor[15]; this effect can be reversed by addition of the cholesterol precursor mevalonic acid. Additionally, hypercholesterolemia in a pig model reduces the endothelium-dependent relaxation to aggregating platelets[16]; thus, hypercholesterolemia may delay the already limited recovery of endothelial cell function after balloon injury.[17] Studies in patients with angiographically normal coronary arteries have confirmed that impairment of endothelium-dependent responses is correlated with serum cholesterol levels.[18] A recent study in the cholesterol-fed rabbit model of restenosis showed a decrease in intimal hyperplasia in animals treated with lovastatin.[19]

The present study has several limitations. Although restenosis was generally confirmed angiographically, it is possible that some asymptomatic patients who did not undergo repeat catheterization were misclassified. The use of fish oil in two thirds of the patients is a potentially confounding factor, although multivariate analysis showed no effect of fish oil therapy on restenosis, and confirmed lipid levels at baseline (before fish oil) and follow-up to be independently predictive of restenosis. Whereas the effect of lipids at follow-up appears more striking, these data were obtained in only a nonrandomly selected subset of the total group (90 of 186 patients). Finally, apolipoprotein levels and levels of lipoprotein (a) were not measured; these may prove to have independent predictive value and may be helpful in explaining the mechanism(s) by which lipids influence restenosis.

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Rationale and Design of a Secondary Prevention Trial of Lowering Normal Plasma Cholesterol Levels After Acute Myocardial Infarction: The Cholesterol and Recurrent Events Trial (CARE)

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Recent clinical trials of primary and secondary prevention of cardiovascular disease have demonstrated that lowering plasma cholesterol decreases the incidence of coronary heart disease in patients with elevated plasma cholesterol. However, it is not known whether patients with established coronary artery disease and normal plasma cholesterol can be benefited. Several previous prevention trials reviewed in this report found that patients who had plasma cholesterol levels at baseline in the upper portion of the eligibility range (e.g., >240 mg/dl) received greater benefit from hypolipidemic diet or drug therapy than patients who had lower plasma cholesterol levels at baseline. The recent availability of drugs that are more potent and less prone to cause adverse reactions than previous regimens permits this important question to be addressed. The Cholesterol and Recurrent Events trial is testing whether pravastatin, a hydroxymethylglutaryl coenzyme A reductase inhibitor, will decrease the sum of fatal coronary heart disease and nonfatal myocardial infarction (MI) in patients who have recovered from a MI and who have normal total cholesterol levels. Fatal cardiovascular disease and total mortality are important secondary end points. The trial is enrolling 4,000 men and women from 80 centers throughout North America, age 21 to 75 years, who have survived MI for 3 to 20 months, who have plasma total cholesterol <240 mg/dl (6.2 mmol/liter) and low-density cholesterol of 115 to 174 mg/dl (3.0 to 4.5 mmol/liter), and who are representative of the general population of patients with MI. Patients are randomized to either active or inactive drug therapy. Active therapy consists of pravastatin, 40 mg/day, designed to achieve an average decrease in low-density lipoprotein cholesterol of approximately 30%, and an increase in high-density lipoprotein of 5%. The average duration of follow-up will be ≥5 years. To protect against a lower than expected rate of recurrent events, the trial will be continued until a predetermined fixed number of coronary heart disease events occurs in the entire cohort so that the original sensitivity of the trial will be maintained.

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There is compelling evidence for a causative role for plasma cholesterol in the development of coronary artery disease. The incidence of coronary artery disease among countries and geographic areas is highly correlated with plasma cholesterol.[1] Within populations, plasma cholesterol levels predict coronary artery disease independently of other influences such as age, sex, blood pressure and other plasma lipids.[2–5] For every 1% increase in plasma cholesterol above about 240 to 250 mg/dl (6.2 to 6.5 mmol/liter), the incidence of coronary artery disease increases by 2 to 3%. In the range of plasma cholesterol, 180 to 240 mg/dl (4.7 to 6.2 mmol/liter), this relation is attenuated, and considerably so at the low end.[2–5] Plasma cholesterol also influences the clinical course of patients with preexisting coronary artery disease. In most of these prospective epidemiologic studies,[2,5–7] as in studies in persons without clinical coronary heart disease,[2–5] there is less effect of plasma total cholesterol or low-density lipoprotein (LDL) cholesterol on reinfarction in patients with plasma total cholesterol <240 mg/dl (6.2 mmol/liter)[5–7] or LDL cholesterol <160 mg/dl (4.1 mmol/liter)[2] than in patients with higher levels. For example, in a study of 2,799 British civil servants who

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*See Appendix for all participating centers.

had preexisting myocardial ischemia, the risk of coronary death increased by only 24% within the baseline plasma cholesterol range of <180 mg/dl (<4.6 mmol/liter) to 220 to 259 mg/dl (5.6 to 6.7 mmol/liter); however, coronary death more than doubled for patients with plasma cholesterol ≥260 mg/dl (6.7 mmol/liter) compared with the next lower category, 220 to 259 mg/dl[5] (Figure 1).

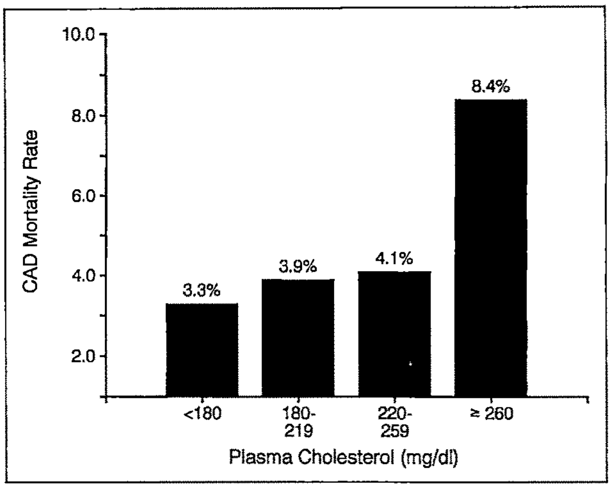

FIGURE 1. Plasma cholesterol and coronary artery disease (CAD) mortality in British men with preexisting CAD (The Whitehall Study). (Adapted from Rose et al.[5])

Clinical trials show that diets or medications that lower elevated plasma cholesterol levels decrease the onset of coronary artery disease in previously healthy persons, and lower the rate of recurrent myocardial infarction (MI) in patients who had previously experienced 1 or more infarcts.[8-18] When the findings in the secondary prevention trials are combined, a relation emerges that links every 10% decrease in plasma cholesterol to a 15% decrease in recurrent MI compared with a somewhat greater reduction of 22% in primary prevention trials.[19] These relationships are derived from experience mostly in patients with hyperlipidemia. Generalization to a population with lower plasma lipids should consider the attenuated influence of plasma cholesterol as a risk factor in the range <240 mg/dl (6.2 mmol/liter).[3-7]

There are several unanswered questions that are critical to knowing how to manage the plasma lipids of patients with coronary artery disease:

1. HYPERLIPIDEMIA VERSUS NORMAL PLASMA LIPID LEVELS: The populations that were studied in previous clinical trials had elevated mean plasma cholesterol levels ranging from 233 to 313 mg/dl (6.0 to 8.1 mmol/liter),[8-18] and >240 mg/dl in all but 1 trial.[9] No trial has focused on patients with plasma cholesterol levels <240 mg/dl. In fact, in primary and secondary prevention trials,[9,10,20,21] subgroups of patients with average initial plasma cholesterol levels of 185 to 230 mg/dl (4.8 to 5.9 mmol/liter) experienced less reduction in recurrent events than subgroups with elevated plasma cholesterol levels of 247 to 305 mg/dl (6.4 to 7.9 mmol/liter). This poses the question of whether plasma cholesterol reduction is of clinical benefit in patients with established coronary artery disease with cholesterol levels <240 mg/dl (Figure 2). This question is particularly pertinent because a large majority of patients

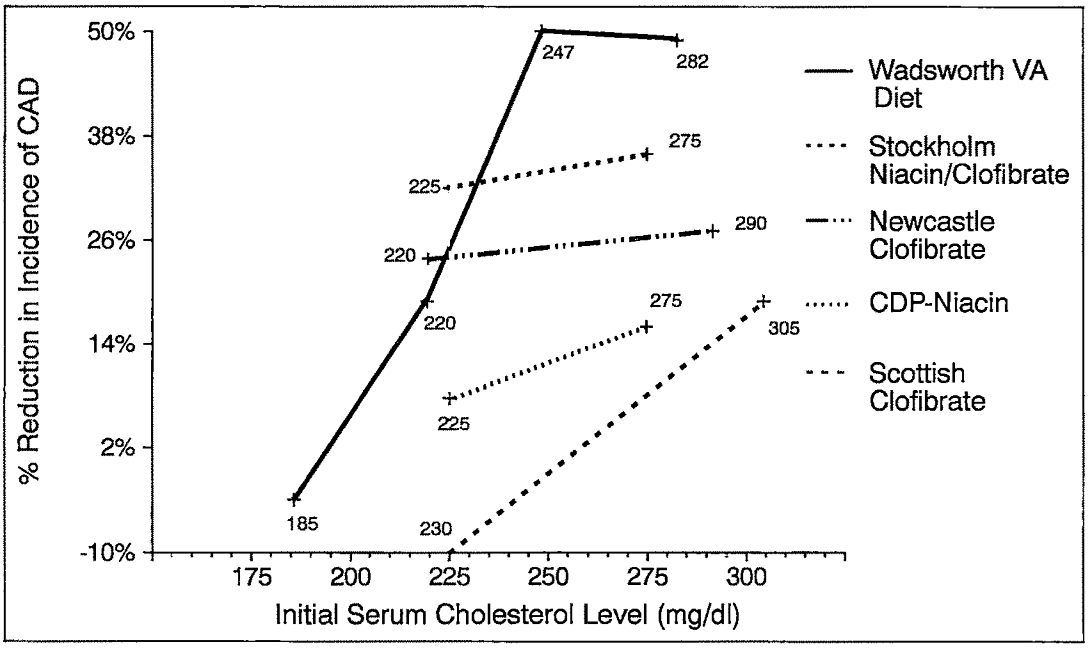

FIGURE 2. Relation between initial serum cholesterol and reduction in coronary artery disease (CAD) in 5 trials of hypolipidemic therapy. All are trials of secondary prevention except the Wadsworth Veterans Administration (VA) trial which included patients with and without coronary artery disease. The individual trials and reference numbers are: Wadsworth VA diet trial,[9] Stockholm clofibrate and niacin trial,[11] Newcastle clofibrate trial,[14] Coronary Drug Project (CDP) niacin trial, [16] and the Scottish clofibrate trial.[10]

with coronary artery disease have plasma cholesterol levels in this range.[2–7]

Plasma triglyceride levels also may influence the effectiveness of hypolipidemic therapy in reducing rates of cardiovascular disease. Patients with mild to moderate hypertriglyceridemia treated with the combination of clofibrate and nicotinic acid,[11] colestipol[12] or gemfibrozil[13] had a greater reduction in events than the patients in the trials who had normal plasma triglyceride levels. Finally, in the Helsinki Heart Study,[13] patients with familial combined hyperlipidemia (elevated plasma total cholesterol, LDL cholesterol and total triglycerides) had a greater reduction in cardiovascular disease than patients with hypercholesterolemia. Combining these findings with observations on patients with different plasma lipid patterns, it appears that in general, the more abnormal the plasma lipid phenotype, the greater the benefits of hypolipidemic treatment.

2. ELDERLY PATIENTS AND WOMEN: It is not clear whether the favorable results from cholesterol lowering trials in selected cohorts of relatively young men can be generalized to a wider population. Most previous trials, and all of the trials with >1,000 patients, excluded older patients; the upper limits for enrollment were 55 years,[13] 60 years,[14,15] and 65 years.[8,16–18] Two small trials with 555 and 717 patients enrolled patients up to age 70 years.[9,11] Only 1 trial, the Los Angeles Wadsworth Veterans Administration Hospital diet study, enrolled elderly patients up to age 90 years (mean 65).[9] In this study, diet therapy reduced the incidence of fatal atherosclerotic end points and reduced all cardiovascular disease events significantly only in the men who were younger than age 65 at entry but not in the older subgroup (Figure 3). A similar effect was found in a trial of colestipol.[12] Most trials of lowering plasma lipids enrolled only men.[9,13–17] Four trials[8,10,11,18] — all on secondary prevention — did not restrict enrollment to men, but together enrolled a total of only 412 women (19% of the trials' patients) because of the low prevalence of coronary heart disease in middle-age women compared with men. Only 1 trial, the colestipol-Upjohn study,[12] enrolled sufficient numbers of women for separate analysis. In the 1,094 men, treatment reduced the mortality from cardiovascular disease significantly from 4.4% to 2.0%, whereas in the 1,184 women, mortality was nearly identical in the treatment and placebo groups (1.5 vs 1.7%). However, the low mortality rate in the women and the relatively short follow-up, 2 years, limits the conclusions from this study on the effect of hypolipidemic therapy in women.

3. IMPROVEMENT IN RATES OF FATAL CARDIOVASCULAR DISEASE OR OF ALL-CAUSE MORTALITY HAS NOT BEEN FOUND IN PRIMARY OR SECONDARY PREVENTION TRIALS OF CORONARY ARTERY DISEASE: The Program of Surgical Control of Hyperlipidemia[8] achieved the largest reduction in plasma cholesterol of any prevention trial — 23% — and found a 35% decrease in the combination of fatal and nonfatal coronary artery disease, which was statistically significant. However, the prespecified primary end point of the trial, the total mortality rate, was not significantly improved. In trials that test therapies that cannot be blinded, total mortality is of paramount importance since its ascertainment is relatively free from bias. Moreover, this trial tested a treatment considered impractical for most patients, partial ileal bypass, and thus cannot be a guide for contemporary therapy. One trial that stands as an exception is the small-scale Stockholm Ischemic Heart Disease Trial.[11] In all, 555 patients with average plasma cholesterol levels of 250 mg/dl (6.5 mmol/liter) were randomized 4 months after MI to the combination of clofibrate and nicotinic acid or to no treatment. After 5 years of follow-up, there were 26% fewer deaths in the treatment group than in the control group, a significant difference. Because only this trial[11] found improved survival in the treatment group at the end of the treatment period, investigators speculated that the excess of nonfatal MI in the control groups of the other trials would eventually result in an excess of deaths if the period of follow-up was extended. For example, the Coronary Drug Project

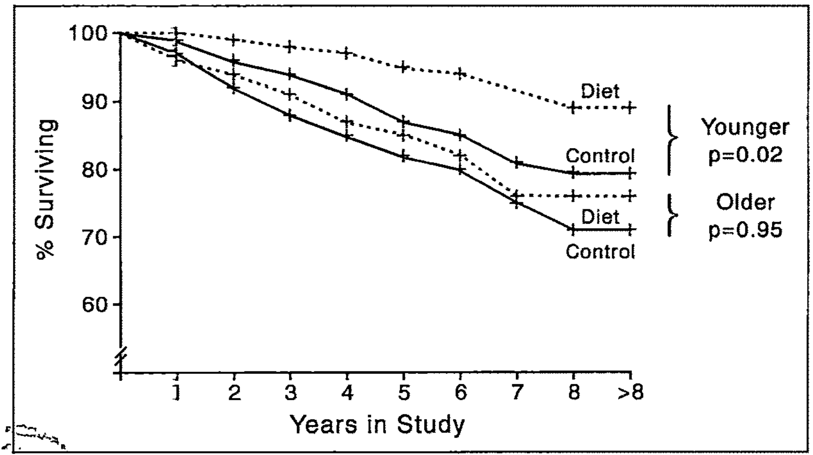

FIGURE 3. The relation between age (<, >65 years) and the decrease in fatal atherosclerotic events in a trial of diet therapy. (Reprinted with permission from Dayton et al. *Circulation* 1969;[suppl II]:II-34–II-35.)

found no trend toward improved survival in the group that received niacin when the trial ended after 6.2 years of treatment.[16] However, extended follow-up for a total of 15 years demonstrated a reduction in the mortality rate of 11% in patients who were originally randomized to niacin compared with those given placebo.[20] In contrast, extended follow-up in 3 other trials that used clofibrate[20,22] or diet[17] did not find a trend toward improved survival.

Perhaps the explanation for lack of a favorable effect on fatal cardiovascular disease and all-cause mortality is a combination of the modest inherent hypolipidemic effect of the drugs or diets, adverse symptoms that reduced compliance, inadequate duration of treatment, or inadequate sample size. All of these problems could have lowered the statistical power of these trials below that needed to detect improved survival. Nevertheless, the disquieting alternative possibility that hypolipidemic drug therapy causes a slight but counterbalancing increase in the rate of serious events other than MI, no matter how counterintuitive, has never been disproved. A meta-analysis of primary prevention trials found just such a significant increase in cancer and traumatic deaths.[23] Adverse effects of drugs that would be taken for many years, probably for a lifetime, could become proportionately more prominent in patients with lower plasma cholesterol levels and lower risk of recurrent cardiovascular events. Unexpected adverse effects caused by clofibrate,[22] estrogen[24] and thyroid hormone[25] in previous trials also argue for a conservative approach to adopting aggressive treatment strategies that require new classes of medications or combinations of drugs without testing in clinical trials. Finally, even if not harmful, the cost of prolonged administration of drugs must be balanced against the benefit, if any.

The present trial is designed to overcome some of the limitations of previous secondary prevention trials. First, entry criteria are designed to enroll a cohort that is representative of the general population of patients who have recovered from acute MI to permit wide application of the results. Both men and women are included. Second, the efficacy of treatment on plasma lipids is expected to be quite substantial. Pravastatin, a highly effective inhibitor of cholesterol synthesis, produces an average decrease in LDL of 30%,[26] which might be projected to lower recurrent cardiovascular disease by 30 to 40%.[19] Moreover, pravastatin does not cause adverse effects such as gastrointestinal symptoms, myopathic syndromes or hepatobiliary disease that are likely to diminish compliance.[26,27] Third, the sample size and effectiveness of the drug therapy permit the trial to address cardiovascular mortality. Finally, to maintain sensitivity, the trial does not have a fixed duration of follow-up, but will continue until a predetermined number of events occur. This will protect the study from a decline in event rates caused by continued advances in therapy of ischemic syndromes.

TABLE I Eligibility Criteria for the Cholesterol and Recurrent Events Trial

- Inclusion criteria
  - Acute MI between 3 and 20 months before randomization
  - Age 21–75 years
  - Men and women (postmenopausal or surgically sterile)
  - All racial and ethnic groups
  - Plasma total cholesterol <240 mg/dl (6.2 mmol/liter)
  - Plasma LDL cholesterol 115–174 mg/dl (3.0–4.5 mmol/liter)
  - Fasting serum triglycerides <350 mg/dl (4.0 mmol/liter)
- Exclusion criteria
  - Ejection fraction <25%
  - Overt congestive heart failure (symptomatic despite drug therapy)
  - Prior sensitivity to HMG-CoA reductase inhibitors
  - History of nonresponsiveness to reductase inhibitors (≤10% decrease in total cholesterol)
  - No coronary atherosclerosis on arteriogram, if performed
  - Nephrotic syndrome or other renal disease
  - Excessive ethanol intake defined as >3 drinks per day
  - Hepatobiliary disease: chronic hepatitis, biliary cirrhosis, alcoholic cirrhosis, other causes of chronic jaundice or significant other hepatic disease (SGOT, SGPT, total bilirubin, or alkaline phosphatase >1.5× ULN for the laboratory)
  - Malignancy or other medical condition thought to limit survival, require radiation or chemotherapy, or interfere with participation
  - History of immune disorders (dysproteinemia, porphyria, lupus erythematosis) or treatment with immunosuppressive agents
  - Untreated endocrine disorders or other uncontrolled endocrine disease
  - Significant gastrointestinal disease or surgery which may interfere with drug absorption
  - Treatment with other lipid-lowering drugs, unless they are withdrawn
  - Severe valvular heart disease requiring surgery
  - Psychosocial condition that would make a person unsuitable for a clinical trial
  - Geographic location, i.e., distance to clinic making attendance difficult or itinerant lifestyle
  - Participation in another drug trial that could affect the end point of this study, or use of any investigational drug within 30 days of enrollment
  - Unwilling to consent

HMG-CoA = hydroxymethylglutaryl coenzyme A; LDL = low-density lipoprotein; MI = myocardial infarction; SGOT = serum glutamic oxaloacetic acid; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal.

Study design: The overall goal of the trial is to determine whether intensive therapy to lower plasma cholesterol will decrease fatal and nonfatal recurrent coronary heart disease, and all-cause mortality in patients who have had an MI, and who have normal plasma cholesterol levels.

Population (Table I): The qualifying MI will have occurred between 3 and 20 months before randomization: (1) in the presence of symptoms of myocardial ischemia or infarction, the development of an elevation of creatine kinase to at least twice the upper normal limit with an associated positive MB band, or a single positive MB test associated with a decrease in the total serum creatine kinase level to 50% of the peak level if also accompanied by sustained T-wave inversions for ≥72 hours in 2 inferior or 2 contiguous anterior leads; and (2) in the absence of ischemic symptoms and elevated creatine kinase, new Q waves ≥30 ms in duration and 0.1 mV in magnitude, in 2 inferior or contiguous

TABLE II Flow Chart for the Prerandomization Period

- Identify and contact prospective eligible patients
- Contact patient's physician to obtain support and information on eligibility
- Diet counseling: confirm that patient received appropriate counseling or begin counseling at a "prescreening" visit
- Screening evaluation (by telephone or in person)
  - Withdrawal of prohibited medications if needed
  - Diet documentation (counseling if needed)
  - Obtain informed consent
  - Schedule eye examination
  - Schedule first qualifying visit
- First qualifying visit
  - ≥8 weeks after hospital discharge
  - Lipid measurements by core laboratory
  - Full laboratory testing
  - Begin run-in period with placebo pills
  - Confirm MI with core facility (send ECG and other data)
  - Confirm ejection fraction ≥25%
  - Obtained informed consent if screening evaluation was by telephone
  - Blood for apolipoprotein or other ancillary lipid or nonlipid assessments
- Second qualifying visit
  - 7 days to 1 month after first visit
  - ≥12 weeks after hospital discharge
  - Qualifying lipid measurements by core laboratory
  - Liver and muscle enzymes (CK), creatinine, thyroid screening, lipoprotein measurement by ultracentrifugation, Hb A1C if glucose ≥220 mg/dl
  - Tablet count
  - Blood for apolipoprotein or other ancillary lipid or nonlipid assessments
- Third qualifying visit (optional for patients with borderline lipid levels):
  - Qualifying lipid measurements by core laboratory
  - Tablet count
- Schedule radionuclide ventriculogram if necessary
- Randomization visit
  - 7 to 42 days after the last qualifying visit
  - Clinical evaluation including physical examination
  - ECG
  - Dietary consultation
  - Tablet count
  - Randomize, give new medication supply

ECG = electrocardiogram; Hb = hemoglobin; MI = myocardial infarction.

anterior leads not present on a previous electrocardiogram in the absence of left bundle branch block, Wolff-Parkinson-White syndrome or paced rhythms.

The inclusion criteria for plasma lipids are plasma total cholesterol <240 mg/dl (6.2 mmol/liter), LDL cholesterol 115 to 174 mg/dl (3.0 to 4.5 mmol/liter), and triglycerides ≤350 mg/dl (4.0 mmol/liter). A plasma LDL cholesterol level of 174 mg/dl (4.5 mmol/liter) corresponds to the 80th percentile in men and women aged 50 to 59 years.[28] Although the upper limit for entry for LDL cholesterol, 174 mg/dl (4.5 mmol/liter), exceeds the threshold for drug therapy (160 mg/dl; 4.1 mmol/liter) advocated in the National Cholesterol Education Program,[29] subgroups of patients in previous clinical trials that had average plasma total cholesterol on entry between 185 and 225 mg/dl (4.4 and 5.8 mmol/liter) had less benefit than subgroups with higher mean plasma total cholesterol between 247 and 305 mg/dl (7.1 and 8.0 mmol/liter)[9,10,20,21] (Figure 2). No trial has focused on patients with levels of plasma cholesterol <240 mg/dl.

Other major inclusion criteria are: (1) age 21 to 75 years, (2) men or women (postmenopausal or surgically sterile), (3) absence of congestive heart failure, and (4) left ventricular ejection fraction ≥25%. Additional criteria are listed in Table I and are designed to exclude patients with serious noncardiovascular disease likely to interfere with participation or to cause death before the trial is over, with contraindications to pravastatin.

Patients otherwise eligible are deferred for randomization until 6 months elapse after coronary angioplasty, and 3 months after coronary artery bypass surgery. The deferment after coronary surgery or angioplasty decreases the likelihood of counting as study end points early graft occlusion or angioplasty restenosis.

Prerandomization period (Table II): SCREENING: The research staff screens patients admitted to the coronary care unit for acute MI, cardiac rehabilitation programs and outpatient cardiology clinics. The patients' personal physicians are made aware of the implications of the double-blind administration of treatment and placebo, the trial's provisions for managing elevated cholesterol levels (described subsequently), and the prohibition of other lipid-lowering medications. The patients' lipid levels after randomization are not released to the patients, their physicians or the investigators at the clinical centers. Patients who give informed consent will take part in a series of 2 to 3 qualifying visits. Documented dietary instruction is a prerequisite for entering screening.

Withdrawal of lipid-lowering agents and other prohibited drugs is required before the formal series of prerandomization visits may begin. Patients must have discontinued therapy with probucol or fibric acid derivatives for ≥12 weeks, hydroxymethylglutaryl coenzyme A reductase inhibitors for ≥8 weeks, and nicotinic acid and other prohibited drugs for ≥4 weeks.

Plasma lipids are measured by the Core Laboratory after 4 weeks of diet treatment, and no earlier than 8 weeks after hospital discharge after MI. Fasting blood is obtained from 7 to 21 days apart on qualifying visits 1 and 2. The average lipid levels on these 2 days is used to determine eligibility.

Techniques of measurement: LEFT VENTRICULAR EJECTION FRACTION: To document eligibility, left ventricular ejection fraction is measured after the qualifying MI either by contrast left or radionuclide ventriculography. Echocardiography may be performed in patients who have not undergone these tests, and have an ejection fraction of ≥40%.

PLASMA LIPIDS: Samples are shipped on the day of collection by overnight express to the core laboratory in insulated containers with gelled refrigerant packs to maintain a temperature of 4°C. Samples arrive in the laboratory within 24 hours after collection, and are analyzed within 24 hours. Six 1 ml aliquots of plasma are immediately frozen at −80°C for subsequent analysis in ancillary studies. All lipid analyses are conducted in a blinded manner. Plasma total and high-density lipoprotein (HDL) cholesterol and triglyceride concentrations are measured directly. LDL cholesterol is estimated by calculating the cholesterol remaining in plasma after subtracting HDL cholesterol and the product of 0.2 times the glycerol-blanked triglyceride concentration.[30] External proficiency testing for the core laboratory is conducted by the Lipid Standardization Program of the Centers for Disease Control and the National Institutes of Health.

OTHER LABORATORY TESTS FOR ELIGIBILITY: At the first qualifying visit, fasting blood is obtained for complete blood count, and a full chemistry panel and thyroxin and urinalysis are performed. At the second qualifying visit, the liver enzyme analysis is repeated as well as any other tests yielding abnormal results. If the fasting blood sugar is ≥220 mg/dl at the first qualifying visit, hemoglobin A1C is measured; >11% constitutes an exclusion. If the thyroxin is abnormal, then thyrotropin is measured. Patients are excluded from the trial if they have persistently abnormal values.

Clinical evaluation including a history, medication use, physical examination and blood pressure is performed by a physician at the randomization visit. Ophthalmic examination is performed generally before enrollment or shortly afterward as required by the Food and Drug Administration.

Run-in period: From the first qualifying visit until the randomization visit (2 to 9 weeks), patients are given placebo or pravastatin. At the randomization visit, satisfactory compliance requires that ≥80% of all pills have been taken.

Randomization: Randomization is performed by the Data Coordinating Center by telephone. The randomization into the 2 treatment groups is stratified only by the center so that there is balance in therapy assignment within each of the participating centers.

Dietary program: A structured dietary program is maintained for the duration of the trial. It is directed by

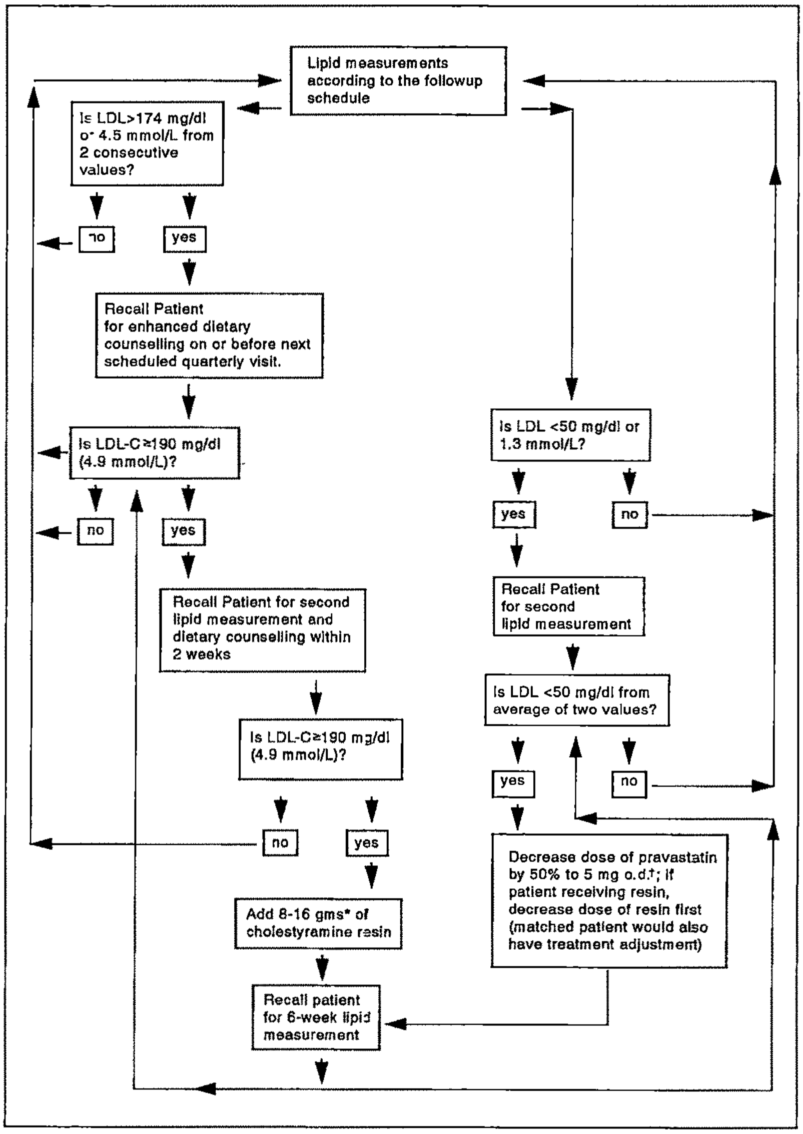
Lipid measurements according to the followup schedule
Is LDL>174 mg/dl or 4.5 mmol/L from 2 consecutive values?
no
yes
Recall Patient for enhanced dietary counselling on or before next scheduled quarterly visit.
Is LDL-C≥190 mg/dl (4.9 mmol/L)?
no
yes
Recall Patient for second lipid measurement and dietary counselling within 2 weeks
Is LDL-C≥190 mg/dl (4.9 mmol/L)?
no
yes
Add 8-16 gms* of cholestyramine resin
Recall patient for 6-week lipid measurement
Is LDL <50 mg/dl or 1.3 mmol/L?
yes
no
Recall Patient for second lipid measurement
Is LDL <50 mg/dl from average of two values?
yes
no
Decrease dose of pravastatin by 50% to 5 mg o.d.†; if patient receiving resin, decrease dose of resin first (matched patient would also have treatment adjustment)

FIGURE 4. Algorithm for managing plasma low-density lipoprotein (LDL) levels in the Cholesterol and Recurrent Events trial. The dose adjustments indicated are either maximums (*asterisk*) or minimums (*dagger*) allowed. Dose changes will be directed by the Data Coordinating Center. Parallel changes in treatment regimen will be made for a matched patient (sex, age by decade, low-density lipoprotein by highest or lowest decile appropriately) in the opposite treatment group to maintain blinding. C = cholesterol; o.d. = every day.

the Clinical Coordinating Center using the approach of the National Cholesterol Education Program.[29] The program at each center is supervised by a registered dietitian. All patients are counseled quarterly. Instructional materials for dietitians and patients, and interim and comprehensive diet questionnaires are provided to the centers. Contact between the coordinating center and the clinical center staff who provide dietary instruction is maintained by a quarterly newsletter and regularly scheduled conference calls. Comprehensive analysis of food and nutrient intake is performed by food frequency questionnaire[31] before randomization and after 1, 3 and 5 years of treatment.

Protocol of drug therapy (Figure 4): PRAVASTATIN: Pravastatin 40 mg as a once per day dose or matching placebo is administered. The expected effect of this dose of pravastatin is to reduce plasma LDL cholesterol by 30%, raise plasma HDL cholesterol by 5%, and decrease plasma triglycerides by 15%.[26] Pravastatin increases the expression of hepatic LDL receptors,[32] thus accelerating the clearance of LDL from the circulation. Pravastatin also decreases the hepatic production rate of very low density lipoprotein, the precursor of LDL, which leads to a decrease in the formation of plasma LDL.[33] Pravastatin is well tolerated. Adverse reactions are few and are primarily mild: skin rash, headache and mild elevations in liver enzymes.[26,27] Neither myopathy nor ocular lens problems have been reported with pravastatin use.

CONTROL OF ELEVATED LOW-DENSITY LIPOPROTEIN CHOLESTEROL: The Data Coordinating Center monitors the levels of the patients and performs the algorithm described subsequently for adjustments of dosage. Although all study patients have baseline LDL cholesterol <175 mg/dl (4.5 mmol/liter), some patients, primarily those taking placebo, may demonstrate LDL cholesterol levels during follow-up that exceed this upper limit. If LDL cholesterol is ≥175 mg/dl on 2 consecutive visits, the patient is scheduled for an interim visit for intensified dietary counseling using the National Cholesterol Education Program Level II protocol.[29] If LDL cholesterol reaches 190 mg/dl (4.9 mmol/liter), cholestyramine resin is prescribed at a daily dose of 8 to 16 g to reduce LDL cholesterol to <175 mg/dl. A matched patient in the other randomized group receives parallel changes in the dietary and cholestyramine treatment.

CONTROL OF HYPERRESPONDERS: If LDL cholesterol decreases to ≤50 mg/dl (1.3 mmol/liter), the dose of pravastatin (or placebo) is decreased by 50%, and the response reassessed in 6 weeks. Parallel changes are made in a patient in the other randomized group.

Monitoring during the treatment phase: A medical history, examination and electrocardiogram are performed annually. Interim evaluation takes place every 3 months for compliance, adverse effects and study end points.

Study end points and major noncardiovascular events are being ascertained at the 3-month visits. Detailed information on the clinical presentation and course is obtained from family and medical records. This information is reviewed by the end points committee without access to treatment assignment or any information that could lead to unblinding.

Duration of the trial: The average duration of follow-up will be ≥5 years. Previous trials of hypolipidemic therapy show that benefit is minimal or nil in at least the first 2 years of follow-up and increases progressively in each successive year.[8,9,11,13,15,16,20,22] Thus, it is considered that a minimum of 5 years is needed to test hypolipidemic therapy. It is possible that advances in medical treatment of ischemic syndromes could lower the event rate in the patients. To preserve the sensitivity of the trial, follow-up will continue beyond 5 years until a fixed number of events occurs in the entire cohort to maintain the original power of the trial. The trial is scheduled to conclude in November 1995.

Sample size determination: Two methods of calculating the sample size were used: (1) comparison of 2 binomial proportions representing the 5-year event rates in the treatment and control groups, and (2) the log rank test. The latter will be used to compare the survival curves. By either method, a sample size of 4,000 subjects will provide a power of ≥85% to detect a 20% decrease in the number of events, and a power of ≥95% to detect a 25% decrease in events due to the therapy, using a 2-sided p value of 0.05.

Analysis of data: OUTCOME VARIABLES: The primary outcome variable is the combination of death from coronary heart disease (fatal MI, sudden death, or death attributable to a diagnostic or therapeutic procedure involving the coronary arterial circulation) and nonfatal MI. The secondary outcome variable is death from coronary heart disease alone, and the tertiary outcome variable is death from all causes. Subsidiary outcome variables include nonfatal MI (definite and probable), need for coronary artery bypass surgery, initial or repeat coronary angioplasty, development of unstable angina, development of overt congestive heart failure, hospitalization for cardiovascular disease, fatal and nonfatal stroke, development of lower extremity atherosclerosis, total coronary heart disease events, and total cardiovascular disease events.

ANALYSIS: The log rank test will be used to compare the survival curves of the treatment and control groups. In addition, Cox regression analysis will be performed with the appropriate interaction term. A subsidiary analysis of end points occurring after the second year of follow-up will be conducted, since previous clinical trials revealed no effect on congestive heart failure outcome variables until after 2 years of follow-up. A number of subgroups have been specified prospectively for analysis of treatment effects: age, gender, race, plasma LDL and HDL, LDL/HDL, triglycerides, ejection fraction, number of previous MIs, months elapsed from MI until enrollment, history of coronary artery surgery or angioplasty, concurrent cardiovascular medications, educational level, obesity, glucose and insulin levels, and intake of dietary fats, carbohydrates, fiber, antioxidant vitamins and minerals, and alcohol.

INTERIM MONITORING: Stochastic curtailment procedures[34,35] will be used to monitor the accumulating data for the trial for either efficacy or harmful effects. This method computes the conditional probability of rejecting the null hypothesis at the end of the trial given the present data and assuming the null hypothesis for the rest of the trial.

Approval for human subjects research: This trial has been approved by the trial's Safety and Data Monitoring Committee, Institutional Review Boards of all participating centers, United States Food and Drug Administration, and the Canadian Bureau of Human Protection.

Trial organization: CLINICAL CENTERS: Each center consists of a primary institution overseeing 1 or more geographically related hospitals and clinics. There are a total of 80 centers: Canada, 13 centers in 6 provinces; and the United States, 67 centers in 40 states. A wide distribution of medical practice settings is represented.

COORDINATING CENTERS: The trial headquarters including the Chairman of the Steering Committee, Principal Investigator, and the Clinical Coordinating Center is located at the Brigham and Women's Hospital and Harvard Medical School. The Clinical Coordinating Center enrolls and trains the clinical centers, monitors enrollment and follow-up, works with the clinical centers to solve problems in trial operations and to enforce the protocol, and authorizes all payments from the sponsor to the clinical centers. The Data Coordinating Center at the University of Texas School of Public Health receives case report forms from the clinical centers and data from the core laboratories, monitors the forms for completeness and consistency, reports to the Clinical Coordinating Center on enrollment and follow-up, performs the randomizations and the interim and final analyses of the data.

SPONSOR: Bristol-Myers Squibb Company provides study medication to the clinical centers, monitors the case report forms at the clinical centers and the supporting documentation to meet regulatory requirements for clinical trials but remains unaware of treatment assignment. The sponsor has no access to the data on lipid changes or end points.

SAFETY AND DATA MONITORING COMMITTEE: The Safety and Data Monitoring Committee consists of experts in biostatistics, clinical trials, cardiology, lipoprotein genetics and metabolism, and cardiovascular epidemiology. The members are not participating in any aspect of trial operations. The committee approves the protocol and any changes, monitors data using both group sequential and stochastic curtailment methods[34,35] and may recommend continuing the trial beyond 5 years, or stopping the trial prematurely for adverse effects of treatment or for early definitive benefit.

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APPENDIX

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Causes and Correlates of Death After Unsupported Coronary Angioplasty: Implications for Use of Angioplasty and Advanced Support Techniques in High-Risk Settings

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To better understand the factors predisposing a patient to death after elective percutaneous transluminal coronary angioplasty (PTCA) and to gain insight into indications for high-risk PTCA both with and without adjunctive use of support devices, the outcomes of 8,052 consecutive procedures were reviewed. Death occurred after 32 procedures (0.4%) and was directly related to coronary artery closure in 26 (81%) of these cases. Left ventricular failure due to vessel closure at the dilated site, the most common cause of death, was independently correlated with female sex ($p < 0.001$), "jeopardy score" ($p < 0.001$) and PTCA of a proximal right coronary artery site ($p = 0.002$), but not with left ventricular ejection fraction or presence of multivessel disease. Right ventricular failure after closure of the proximal right coronary artery, and left main coronary dissection accounted for the majority of the remaining deaths. Systolic blood pressure immediately after coronary artery closure was also closely correlated with jeopardy score, and cardiogenic shock was frequent in women with scores ≥3.5 and in men with scores ≥5.0. These data highlight the superiority of the jeopardy score versus ejection fraction in the determination of risk, stress the importance of gender in determining outcome and point to the need for better means of right ventricular protection from severe ischemia. Therefore, an initial framework for rational use of PTCA and support devices in the high-risk setting is established.

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Several large scale studies have previously assessed the risk of death during elective percutaneous transluminal coronary angioplasty (PTCA),[1-3] and found female sex, multivessel disease and poor left ventricular function to be relative risk factors for that outcome. Given that there were relatively few deaths in those series and that much of the data reported comes from an era of relatively nonaggressive use of PTCA, it is difficult to assess the absolute risk of death in various subgroups of patients. Such an analysis is needed for rational use of PTCA and newly available angioplasty support techniques in high-risk settings. To better define the causes and correlates of cardiac death after elective PTCA, we reviewed the combined experiences of 3 high-volume PTCA centers.

METHODS

Patient population: From January 1, 1984, to June 30, 1989 (San Francisco Heart Institute), from January 1, 1984, to July 1, 1986 (Emory University Hospital), and from January 1, 1987, to June 30, 1989 (University of Michigan Hospital), 8,052 consecutive unsupported PTCAs were performed for indications of stable or unstable angina, or of demonstrable myocardial ischemia. Procedures performed in the setting of acute myocardial infarction (typical ischemic chest pain ≥30 minutes with associated electrocardiographic changes) or with support devices other than intraaortic balloon counterpulsation were not included in this study. Data on procedures performed at the University of Michigan before 1987 had not been entered into a computerized databank, and those performed at Emory University after July 1986 were not available for analysis. Data from 4,242 of these procedures have been reported previously.[1] Three hundred eighty-nine (4.8%) of these 8,052 procedures resulted in acute coronary closure, defined as procedure-related ischemia resulting in cardiac death, emergency coronary artery bypass graft surgery, emergency repeat PTCA, or myocardial infarction, occurring at any time during hospitalization. Patients in whom ischemia resulted solely from closure

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of a side branch[4] were excluded. Twenty-six patients with acute closure had cardiac death (death in which congestive heart failure, myocardial ischemia or cardiac arrhythmias were directly contributory), and their records were compared with those of every third patient with nonfatal closure. Six patients died under circumstances that were related to PTCA, but in which cardiac complications were not believed to be directly causative (pulmonary embolus [2], intracerebral hemorrhage [2], sepsis [1] and anaphylactic shock [1]).

Coronary angioplasty procedure: The technique of PTCA used here has been described elsewhere.[5] Management of patients with acute closure syndrome was performed on an individualized basis. In general, however, if the occlusion occurred while at the cardiac catheterization laboratory, an attempt was made to redilate the area of closure. Intraaortic balloon pump support or "bail-out catheter"[6] placement (when available), or both, were used at the discretion of the operator. If the arterial closure occurred after transfer from the cardiac catheterization laboratory, the patient was generally returned for an attempted PTCA if the first dilation had produced an initially satisfactory result. The patient was sent immediately to the operating room if the initial dilation had resulted in a large dissection or if other technical factors associated with the initial procedure suggested that repeat dilation would likely be unsuccessful.

Data collection and entry: Demographic and clinical information, angiographic and PTCA measurements, and data after PTCA were recorded prospectively during hospitalization on standard forms by a physician. This information was audited for completeness and entered into computerized databanks at Emory University, San Francisco Heart Institute and the University of Michigan. The data were forwarded to the central University of Michigan databank for analysis. Further angiographic information was obtained by retrospective review of the patients' charts or cineangiograms, or both, by a reviewer unaware of the clinical outcome. The following variables were evaluated to ascertain their relation to cardiac death and systolic blood pressure after abrupt coronary artery closure: age; bail-out catheter use; closure score; diabetes; gender; intraaortic balloon catheter use; jeopardy score; left ventricular ejection fraction; multivessel disease; prior bypass surgery; prior myocardial infarction; procedure date; and vessel site dilated.

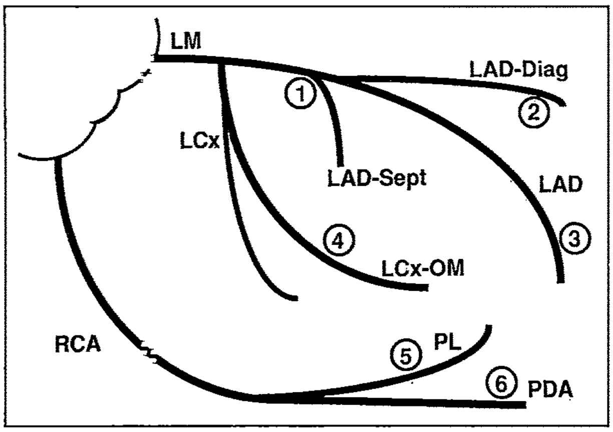

FIGURE 1. Myocardial segments assessed in determination of jeopardy score. Right dominant coronary system is shown. Diag. = diagonal; LAD = left anterior descending; LCx = left circumflex; LM = left marginal; OM = obtuse marginal; PDA = posterior descending artery; PL = posterolateral; RCA = right coronary artery; Sept = septal. (Adapted from Califf et al.[7])

Definition of terms: Cardiogenic shock was defined as systolic blood pressure <80 mm Hg and unresponsive to immediate resuscitative measures.

Multivessel disease was defined as $\geq 50\%$ diameter stenosis in ≥ 2 major epicardial arteries or a bypassable branch thereof.

Closure score and jeopardy score (Figure 1) have been previously defined[1] and are based on the prior work of Califf et al[7] and Kalbfleisch and Hort.[8] In these scoring systems, the coronary tree is divided into 6 segments of approximately equal myocardial perfusion. A score of 0.5 is given for each area of myocardium corresponding to a coronary segment that is hypokinetic and would not be affected by closure at the site dilated. A score of 1.0 is given to each area that is likely to become akinetic or dyskinetic in the event of closure of the dilated coronary stenosis. Closure score is the sum of scores for the 6 areas if the vessel dilated were to close (assuming the myocardium perfused by that vessel were to become akinetic), and jeopardy score is the sum of scores that would result if the myocardium subserved by the vessel dilated and all stenosis $\geq 70\%$ (by calipers) were to become akinetic.

Statistical analysis: Data are presented as mean ± 1 standard deviation unless otherwise stated. Chi-square and Student's *t* tests were used to assess differences in categorical and continuous variables, respectively (Table I). Multiple regression analyses were used to determine the independent correlates of cardiac death and systolic arterial pressure after coronary closure. Statistical significance was assumed when the null hypothesis could be rejected with 95% confidence. Data presenting absolute risk of death (Table II) were determined under the assumption that the subpopulation of patients surviving abrupt arterial closure were representative of that entire group (each survivor was counted 3 times for this analysis because only every third patient with nonfatal closure was elevated for the purposes of this analysis [see Methods]).

RESULTS

Overall outcome: Three hundred eighty-nine (4.8%) of 8,052 procedures resulted in closure of the dilated

TABLE I Correlates of Cardiac Death After Acute Vessel Closure

	Patients Who Died (n = 26)	Patients Who Survived (n = 121)	Univariate 2-Tailed p Value	Multivariate 2-Tailed p Value*
Clinical variables				
Age (yrs)	63 ± 8	58 ± 9	0.01	NS
Diabetes mellitus (%)	23.1	12.4	0.13	NS
Female gender (%)	73.1	27.3	<0.001	<0.001
Prior bypass surgery (%)	7.6	6.7	NS	NS
Prior myocardial infarction (%)	57.7	44.5	NS	NS
Angiographic variables				
Closure score	2.8 ± 1.0	2.2 ± 0.1	0.006	NS
Ejection fraction ≤40%	23.1	17.6	NS	NS
Ejection fraction ≤25%	3.8	0.8	NS	NS
Jeopardy score	3.5 ± 1.2	2.5 ± 1.2	≤0.001	<0.001
Multivessel disease (%)	73.1	55.8	0.06	NS
Procedural variables				
"Bail-out" catheter placed (%)	7.6	9.0	NS	NS
Emergency bypass surgery (%)	61.5	65.3	NS	NS
Proximal left anterior descending stenosis dilated	26.9	20.7	NS	NS
Proximal right coronary artery stenosis dilated (%)	26.9	7.4	0.004	0.002

*Coefficients: female sex = 0.30; jeopardy score = 0.09; proximal right coronary artery stenosis dilated = 0.31; constant = −0.19; multiple r^2 = 0.30; F ratio = 18.7; 2-tailed p value ≤0.001.
NS = not significant.

TABLE II Correlation of Jeopardy Score with Risk of Death After Abrupt Closure

Jeopardy Score	Mortality
≤2.0	2.3%
2.5–3.0	10.0%
3.5–5.0	11.5%
5.5–6.0	33.3%

TABLE III Correlation of Jeopardy Score with Blood Pressure After Abrupt Arterial Closure*

Jeopardy Score	Men	Women
≤2.0	113 ± 20	109 ± 15
2.5–3.0	117 ± 13	81 ± 24
3.5–4.5	96 ± 7	65 ± 4
5.0–6.0	75 ± 5	68 ± 13

*mm Hg in patients for whom this data was available.
For both jeopardy score and sex, p <0.001 by analysis of variance.

stenosis leading to death, myocardial infarction, or need for emergency bypass surgery or PTCA. Twenty-six patients (0.3% of all patients treated) suffered a consequent cardiac death.

Causes of death: The primary causes of death were: left ventricular failure consequent to closure of the dilated stenosis (13 patients, 41%); right ventricular failure consequent to closure of the dilated stenosis (5, 16%); left main dissection (4, 13%); multisystem failure with contributing left ventricular failure after emergency bypass surgery (3, 9%); and sudden death (1, 3%). Six patients (18.3%) died owing to causes not directly related to coronary artery closure.

Of patients dying of left ventricular failure, 81% were women, mean jeopardy score was 3.4 ± 1.6, 75% had multivessel disease, 69% had a prior infarct, and 38% had a left ventricular ejection fraction ≤40%. Of patients dying of right ventricular failure, all had PTCA of the proximal right coronary artery, none had a left ventricular ejection fraction <50%, 80% were women, mean jeopardy score was 3.4 ± 1.7, and 40% had multivessel disease (both patients had 2-vessel disease). Only 1 patient had severe pulmonary disease.

Clinical characteristics and correlates of death after acute closure: The incidences of each of the 5 clinical, 5 angiographic and 4 procedural variables in the group of patients who died and in the subgroup who survived, as well as the corresponding levels of statistical significance, are reported in Table 1.

There were 5 significant univariate correlates of cardiac death: female sex (p <0.001); jeopardy score (p <0.001); dilation of proximal right coronary artery (p = 0.004); closure score (p = 0.006); and age (p = 0.01). Of these, female sex, jeopardy score and dilation of proximal right coronary artery were independently correlated with cardiac death (Table I).

Hemodynamic consequences of acute closure: Systolic blood pressure after acute closure, but before use of intravenous pressors or the intraaortic balloon pump (when available for analysis), was strongly and independently correlated only with jeopardy score and sex (see Table III).

DISCUSSION

Appropriate use of PTCA and related support devices requires an understanding of the causes and correlates of cardiac death with unsupported PTCA. The current study is the largest recent series to address these issues and considerably extends previous work in several areas.

Prior studies have suggested that female sex, poor left ventricular function and multivessel disease are important in the genesis of PTCA-related mortality, but they have not provided an estimate of the likelihood of death for a given patient based upon that patient's clinical and anatomic presentation.[1-3] The major findings of this study are: (1) The primary cause of death in almost one half of fatal procedures was left ventricular failure consequent to closure of the dilated stenosis, and its likelihood was strongly and directly related to the left ventricular jeopardy score ($p < 0.001$) and the patient's sex ($p < 0.001$). The overall risk for this occurrence can be approximated by adding the coefficients in Table I. Importantly, risk of fatal left ventricular failure was not closely correlated with baseline ejection fraction or the presence of multivessel disease, presumably because of the greater importance of the sum of the acutely nonfunctional and baseline nonfunctional myocardial territories. (2) The second most frequent cause of cardiac death, occurring in 16% of fatal procedures, was right ventricular failure. It occurred exclusively with abrupt closure of proximal right coronary artery stenosis ($p < 0.001$) and was more frequently seen in women ($p = 0.01$). None of these patients had a baseline left ventricular ejection fraction <50%. (3) The third most frequent cause of death, accounting for 13% of fatal outcomes, was left main dissection. Its occurrence in this series of patients selected for the absence of overt left main coronary disease was largely unpredictable. (4) Immediate cardiogenic shock occurred infrequently, except when jeopardy score was ≥5.0 (men) or ≥3.5 (women).

These findings have several implications in an era when various percutaneous left ventricular support devices are becoming available for clinical practice. First, because cardiac deaths after PTCA can be related to the amount of potentially jeopardized left ventricular myocardium and to the patient's sex (with the exception of deaths related to right ventricular failure and left main dissection), preliminary strategies for the application of such support devices can possibly be rationally applied (Tables II and III). For example, percutaneous cardiopulmonary bypass support, which can provide 4 to 6 liters/min of cardiac output for up to 6 hours, is currently considered to be possibly indicated for patients with left ventricular ejection fractions of 25%, or for those undergoing PTCA of a vessel supplying more than one half of the myocardium, or both, who are not good candidates for bypass surgery.[9] When this strategy was used in 105 consecutive patients, an in-hospital mortality of 7.6% resulted, and major peripheral vascular complications occurred in 7.2% of the survivors.[9] It is uncertain how many of these patients actually needed the support device for hemodynamic support. Data from the present study suggests that jeopardy score is a better estimate of risk than ejection fraction and that prophylactic support may be indicated only for women with jeopardy scores >3.0 and for men with jeopardy scores ≥5.0, because of the risk of immediate refractory hemodynamic collapse and death during vessel closure in these settings. Arterial and venous access without 18Fr cannulation may be advocated for women with jeopardy scores of 3.0 and for men with jeopardy scores of 3.0 to 4.5, because of the considerable mortality, but lessened incidence of immediate cardiogenic shock, in the event of abrupt vessel closure in such patients. Patients in either of these subgroups should probably not undergo PTCA without the availability of this or another support device and should certainly be considered strongly for coronary bypass surgery instead of PTCA. However, these indications would also need to be based upon the somewhat predictable likelihood of abrupt arterial closure,[5,10] to be considered preliminary and to be modified by further clinical experience. The level of hemodynamic support provided by other devices, such as the hemopump[11] and coronary sinus retroperfusion,[12] is less well defined, and such a scheme would have to be altered based on experience with these devices. Furthermore, because none of these devices can be expected to appreciably reduce right ventricular dysfunction consequent to proximal right coronary artery occlusion, dilatation of high-risk[5,10] proximal right coronary artery stenoses should be performed with particular caution. Further development of right ventricular support devices is needed. Additionally, given that left main dissection accounts for 13% of all cardiac deaths and that "crash-on" cardiopulmonary support can be effective in patients with cardiogenic shock and left main dissection,[13,14] it can be argued that cardiopulmonary support should be available for emergency use in all cardiac catheterization laboratories with a moderate or large volume of coronary angioplasties.

These results should be viewed with an understanding of the limitations of this study. First, this is a retrospective analysis and not all patients received "state-of-the-art" treatment of abrupt closure—use of dilation balloons that allow for distal perfusion,[15] or "bail-out catheters."[16] Future availability of "perfusion-assist" devices such as intracoronary stents may also modify these results. Second, death should not be considered the only major adverse sequelae of abrupt closure, and consideration of infarct size or resultant congestive heart failure was not possible because of the nature of this study. Third, the number of deaths examined was relatively small, and multiple analyses were performed, leading to the possibility of identification of spurious correlations. Fourth, only a minority (40%) of patients with abrupt closure in this study could be considered high risk. Further experience, especially with high-risk patients, will be needed to "fine-tune" the indications for supported PTCA. Fifth, these new support devices cannot be expected to provide equal hemodynamic support or coronary flow, or have the same incidence of clinically significant complications; therefore, these data can provide only an initial framework for their rational use. Sixth, it must be recognized that some abrupt closures after PTCA occur after the "window of protection" provided by these devices. Seventh, it must be understood that hemodynamic support provided by some of these devices does not infer cardiac viability in the event of prolonged interruption of coronary flow, and one must consider the potential availability, or lack thereof, of permanent cardiac support (i.e., cardiac transplantation). Finally, these data should not be construed to imply that supported PTCA is a better treatment alternative than coronary bypass surgery for those patients who would be eligible for both procedures.

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Value of Transesophageal Echocardiography During Complex or High-Risk Coronary Interventions in the Cardiac Catheterization Laboratory

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The increasing complexity of coronary intervention and the limitations of hemodynamic and electrocardiographic monitoring have facilitated the introduction of new imaging techniques in the cardiac catheterization laboratory. Transesophageal echocardiography (TEE) has proved valuable for left ventricular (LV) monitoring during high-risk surgery, but its reported use in the cardiac catheterization laboratory has been limited. Accordingly, we assessed the feasibility and value of TEE during complex or high-risk coronary intervention in the catheterization laboratory.

The TEE probe was successfully introduced in 53 of 54 (98%) attempted cases. The primary imaging goals were LV monitoring in 39 (74%), left main coronary artery (LMCA) imaging in 9 (17%) and both in 5 (9%) cases. LV monitoring was successful in 43 of the 44 (98%) attempted cases. In 25 (58%) of these, additional important observations were made by TEE that were not apparent by symptoms, or hemodynamic, electrocardiographic or radiographic monitoring. These included unexpected changes in regional myocardial function ($n = 20$), alteration in LV size ($n = 2$), exclusion of considered pericardial tamponade ($n = 2$) and detection of unsuspected mitral regurgitation ($n = 1$). Management of the interventional procedure was directly influenced by the findings of TEE in 11 of the 43 (26%) monitored cases. The LMCA was successfully visualized in 13 of the 14 (93%) attempted cases. In 11 of these, measurement of the stenotic lesion diameter by TEE correlated well with quantitative angiography both before ($r = 0.83$, standard error of the estimate $= 0.01$, $p < 0.002$) and after ($r = 0.80$, standard error of the estimate $= 0.03$, $p < 0.005$) intervention. All patients tolerated TEE well without complications.

TEE during complex or high-risk coronary intervention is a feasible, safe and valuable tool for rapid detection of altered myocardial function and thus may influence clinical decisions during interventional procedure. In patients undergoing LMCA intervention, TEE accurately measures stenotic lesion diameter before and after intervention, providing a feasible noninvasive means for follow-up.

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As the complexity and clinical risk of coronary interventional procedures increase, the sensitivity and accuracy of the methods used for monitoring these procedures become increasingly important. The traditional methods of hemodynamic and electrocardiographic monitoring have several limitations. Myocardial ischemia may be asymptomatic, with either unchanged or nonspecific electrocardiographic appearance, and measurements of aortic, pulmonary artery and pulmonary capillary wedge pressures may be misleading since they are frequently altered by vasoactive medications. Localization of the culprit ischemic zone during the course of multivessel coronary intervention may be difficult without direct observation of regional myocardial function. These limitations have facilitated the introduction of new imaging techniques to assist in interventional decision making in the catheterization laboratory.[1-3] Transesophageal echocardiography (TEE) has been found to be more sensitive than either hemodynamic or electrocardiographic monitoring in detecting myocardial ischemia when used for intraoperative left ventricular (LV) monitoring.[4-8] However, its safety and use during complex or high-risk coronary interventions in the cardiac catheterization laboratory have not been reported. Accordingly, we studied the feasibility and value of TEE for detecting myocardial

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ischemia and other procedural events during complex or high-risk coronary interventions. We also explored the accuracy of TEE in measuring left main coronary artery (LMCA) stenosis before and after revascularization intervention.

METHODS

Patients and procedure: Between October 1988 and August 1990, we attempted TEE during 54 complex or high-risk coronary interventional procedures involving 52 selected patients. Increased complexity or clinical risk was related to multivessel coronary intervention, coronary intervention supported by either percutaneous cardiopulmonary bypass or coronary sinus retroperfusion, mechanical coronary atherectomy, revascularization of the LMCA or intervention in patients in cardiogenic shock. All procedures were performed in the cardiac catheterization laboratory. No patient had a history of dysphagia or known esophageal disorders. Institutional Review Board approval for the procedures was obtained. The TEE procedure was explained before elective procedures and informed consent was obtained in all cases. A commercially available echoprobe incorporating a 5 MHz transducer coupled with a Sonos 500 ultrasound system (Hewlett-Packard Corporation) were used. An experienced physician and an ultrasound technologist were involved in the TEE examination.

All patients were customarily premedicated with intravenous diazepam (3 mg) and hydromorphone (1 mg). Arterial and venous sheaths, as well as percutaneous bypass support cannulas, when required, were introduced before intravenous administration of 10,000 U of heparin. An additional intravenous dose of diazepam (5 mg) was given and oropharyngeal anesthesia was provided by 20% benzocaine spray before introduction of the TEE probe. While in a supine position with the head slightly raised, the echo-probe was advanced into the stomach and the best LV short-axis view at the papillary muscle level was obtained for LV monitoring. For LMCA imaging, the echo-probe was withdrawn into the esophagus to a level just below the left atrial appendage. After conclusion of the coronary intervention, and after completion of all electrocardiographic, hemodynamic and angiographic assessments, the echoprobe was withdrawn. Although no oropharyngeal drying agents were used, frequent oral suction was provided throughout the procedure. Whenever possible, the ultrasound system was positioned in proximity to the arterial pressure and electrocardiographic displays to allow the interventional cardiologist to view the images.

Data analysis: A primary indication for TEE monitoring was established in each case before initiation of the interventional procedure. A detailed log documented the procedural stage, significant TEE observations and the immediate influence of these findings on interventional decision making. The electrocardiographic and hemodynamic data corresponding to the echocardiographic findings were also recorded. All TEE images were recorded on ½-inch videotape. The tape audio track was used for precise timing of the procedural events. All echocardiograms were subsequently reviewed by 2 echocardiographers for quality of image, success in accomplishing the primary TEE goal, and the validity of the echocardiographic observations obtained during the procedure. Segmental LV wall motion was subjectively graded as displaying normal wall motion, hypokinesia, akinesia or dyskinesia. Measurements of LMCA stenotic lesion diameters were obtained from still-frame TEE images. The location of the greatest stenosis was identified and its diameter was manually measured using the ultrasound device's analysis software. The stenotic lesion diameter was measured using quantitative angiography (ARTREK®) by an independent investigator blinded to the TEE data. Measurements were obtained by both techniques before and after intervention. All patients were monitored during their subsequent hospital course for complications potentially related to TEE instrumentation.

Statistical analysis: Mean values ± standard deviation were used to report all quantitative variables. A p value ≤ 0.05 was considered statistically significant. Linear regression analysis was used to correlate measurements by TEE and quantitative angiography of LMCA stenosis. The Student's paired t test was used for comparison of measured LMCA stenoses before and after intervention.

RESULTS

Procedural outcome: The introduction of the TEE probe was successful in 53 of 54 attempts, involving 51 patients (40 men and 11 women aged 63 ± 11 years). Coronary interventional procedures included angioplasty supported by peripheral cardiopulmonary bypass ($n = 17$) or coronary sinus retroperfusion ($n = 4$), mechanical rotational atherectomy ($n = 14$), transluminal extraction atherectomy ($n = 11$), unsupported LMCA angioplasty ($n = 2$) and emergent cardiac catheterization and balloon angioplasty in patients in cardiogenic shock ($n = 5$). The target coronary arteries were the LMCA in 17, left anterior descending in 21, left circumflex in 5, right in 12, and coronary bypass grafts in 4 patients. Multivessel intervention was performed in 6 patients. The primary indication for TEE imaging was LV size and wall motion monitoring in 39, LMCA imaging in 9, and both in 5 patients.

TEE was well tolerated by all patients, with no procedural interruption required. Performance of TEE did

TABLE I Clinically Important Events Detected by Transesophageal Echocardiography During Coronary Intervention*

	CPS-Int.	MRA	TEC	CS-R	C. Shock	Total
Myocardial dysfunction after guiding catheter placement	1	4	1			6
Myocardial dysfunction after guidewire placement	2	1				3
Late myocardial dysfunction after angiographically successful intervention	1	1	2			4
Functional data and wall motion changes in cardiogenic shock					5	5
Decrease in LV size			2			2
Enhanced contractility of remote myocardium	1	1				2
Improved contractility in target region	1			1		2
Exclusion of pericardial effusion			1		1	2
Mitral regurgitation					1	1
Total						27

*Echocardiographic findings provided by transesophageal echocardiography not reflected by clinical, hemodynamic, electrocardiographic or angiographic monitoring.
CPS-Int. = cardiopulmonary bypass-supported interventions; CS-R = coronary sinus retroperfusion-supported interventions; C. Shock = cardiogenic shock; LV = left ventricular; MRA = mechanical rotational atherectomy; TEC = transluminal extraction catheter atherectomy.

not significantly prolong the interventional procedures. The cost of TEE was included in the total cost of the procedure; therefore, a cost analysis was not performed. No adverse effects attributable to TEE were detected during or following the procedure.

Left ventricular monitoring: Adequate TEE images were obtained and successful LV monitoring was accomplished in 43 of 44 attempts. In 25 of these patients, additional information regarding 27 intervention-related events was provided (Table I). These events were not heralded by symptoms, electrocardiographic or hemodynamic alterations. Regional myocardial dysfunction in the distribution of the target vessel was observed after guiding catheter placement in 6 patients. In these patients, segmental wall motion deteriorated from normal to hypokinesia or akinesia. In 2 patients, TEE excluded the clinical consideration of pericardial tamponade as a potential cause of acute hemodynamic instability. Previously undiagnosed significant mitral regurgitation was found in 1 patient. An interesting, but not yet clinically useful, observation was made in 4 cases of enhanced myocardial echogenicity noted in the distribution of an injected vessel (3 during rotational atherectomy and 1 after balloon dilation).

In 11 patients, TEE observations directly influenced the course of the interventional procedure. In the 4 cases where TEE identified regional myocardial dysfunction appearing unexpectedly (n = 2) or persisting well beyond the usual time for functional myocardial recovery (n = 2) after an apparently successful angioplasty, repeated angiography of the vessels revealed flow-limiting intimal dissections. Repeated prolonged balloon dilations were then performed with successful restoration of regional contractility (Figure 1). In 1 patient, enhanced contractility of a previously akinetic region suggested hibernating viable myocardium; therefore, angioplasty of the severely stenosed vessel was performed in an attempt to augment local perfusion. In 2 patients with diminished LV size, administration of intravenous fluids restored LV size and preload. In 4 of the 5 patients in cardiogenic shock, inability to improve contractility, despite repeated balloon dilations and the absence of other identified correctable lesions, contributed to the decision not to proceed with further intervention. Shortly thereafter these 4 patients died.

Left main coronary artery imaging: Accurate measurement of LMCA stenotic lesion diameter by TEE before and after intervention was possible in 11 of the 13 patients in whom LMCA imaging was achieved (Figure 2). Stenotic lesion diameter measured by TEE was improved by intervention from 1.2 ± 0.2 to 2.4 ± 0.6 mm ($p < 0.001$) and by quantitative angiography from 1.1 ± 0.3 to 2.0 ± 0.5 mm ($p < 0.001$). LMCA stenotic lesion diameter measurements by TEE correlated well with those obtained by quantitative angiography before and after intervention ($r = 0.83$, SEE = 0.01, $p < 0.002$; $r = 0.80$, SEE = 0.03, $p < 0.005$, respectively) (Figure 3). Measurements by TEE of both lesion diameters before and after intervention were equal to or slightly greater than those obtained by quantitative angiography.

DISCUSSION

Echocardiographic monitoring of left ventricular function during coronary intervention: Transthoracic echocardiography has been successfully used in the cardiac catheterization laboratory in conjunction with coronary intervention.[9] Suboptimal imaging due to the patient's supine position and interference with fluoroscopy hinders the use of continuous monitoring in such a setting and thus generally restricts its use to clinical investigations. TEE effectively circumvents these obstacles, and additionally allows visualization of structures previously not well seen such as the LMCA[10,11] and the left and right atria.[12] The capabilities of TEE to monitor ventricular function continuously have been widely used by anesthesiologists who for several years have been applying this technique during high-risk surgery.[4–8,13,14]

Our results indicate that continuous TEE imaging during high-risk coronary intervention is feasible and often provides valuable clinical information. The proce-

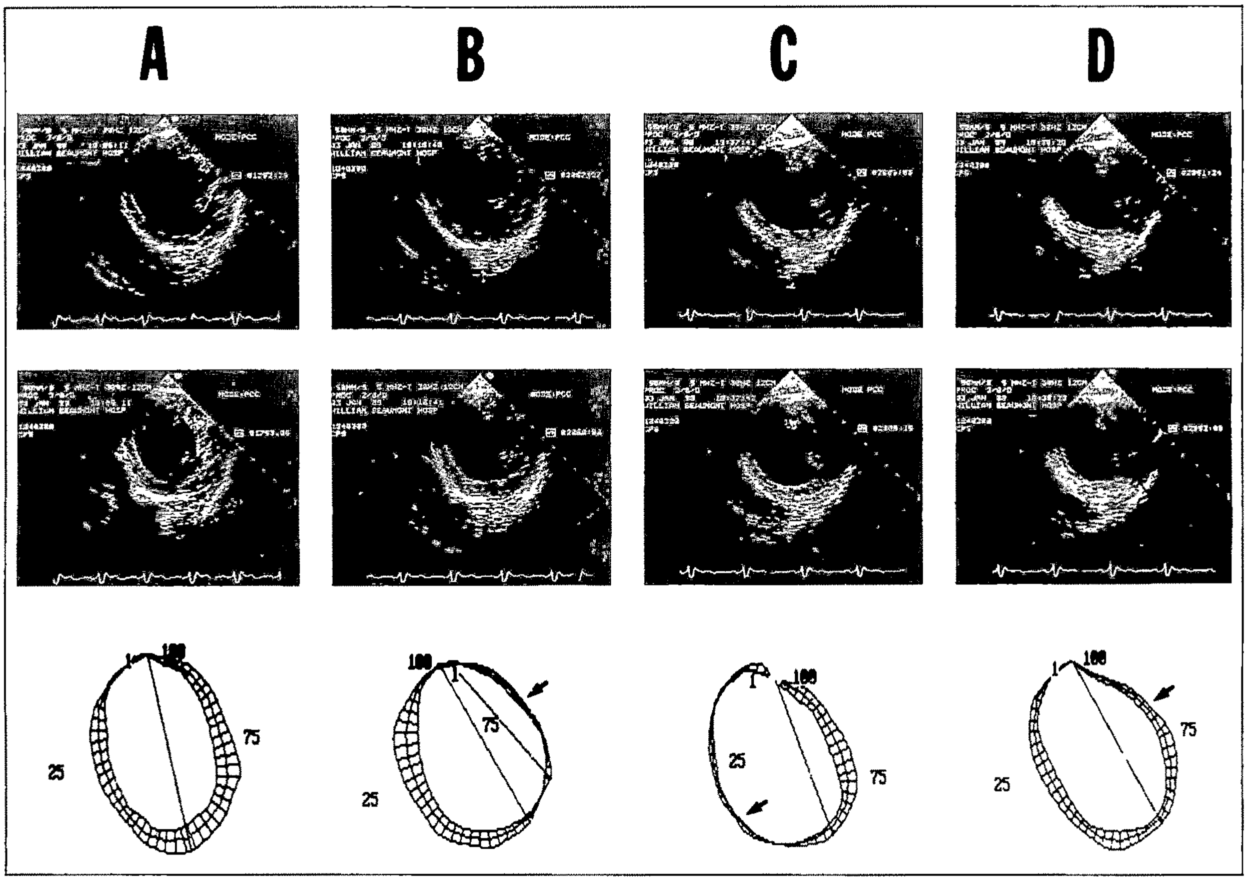

FIGURE 1. Sequential transesophageal echocardiographic findings during 2-vessel angioplasty during cardiopulmonary bypass in a 46-year-old patient with marked baseline left ventricular dysfunction (ejection fraction 15%). Left ventricular cross-sectional view is seen in diastole *(top row)*, systole *(middle row)* and endocardial tracing in both diastole and systole *(bottom row)*. ***A,*** baseline; ***B,*** during balloon inflation in the left circumflex coronary artery, the inferior and lateral walls *(arrow)* became akinetic; ***C,*** during balloon inflation in the left anterior descending coronary artery, the anterior and septal walls *(arrow)* became akinetic; ***D,*** after completion of angioplasty, the lateral wall *(arrow)* is hypokinetic compared with baseline. Repeated angiography of the circumflex coronary artery revealed an occlusive intimal dissection, prompting recrossing and prolonged dilation of the lesion with a good final angiographic and functional result.

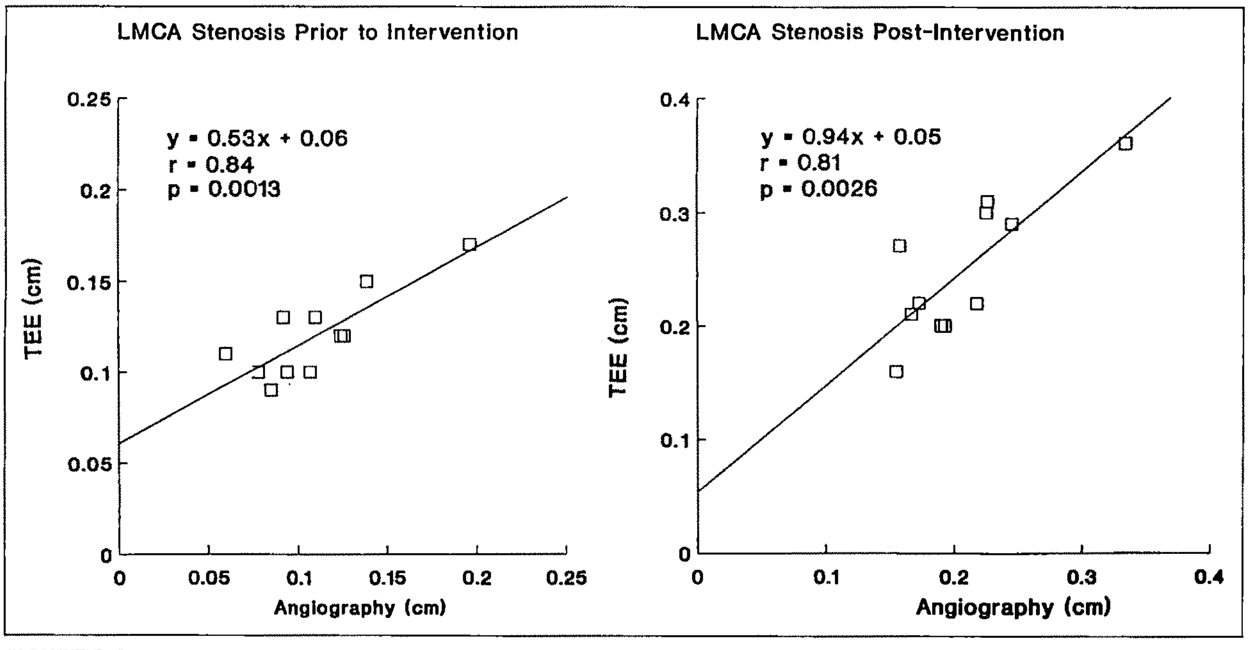

FIGURE 2. Left main coronary artery (LMCA) stenosis diameter before *(left)* and after *(right)* intervention by transesophageal echocardiography (TEE) and quantitative angiography.

dure may be accomplished in almost all cases without interruption due to procedural intolerance. An experienced operator, adequate patient sedation and comfort measures facilitate the examination.

Optimal echocardiographic imaging by TEE was achieved in almost all patients, with continuous display of LV function provided in 43 of the 44 (98%) in whom LV monitoring was desired. Importantly, otherwise unavailable information was also provided by TEE in 58% of these patients. Induction of regional myocardial dysfunction due to guiding catheter or guidewire placement occurred frequently (21%), was asymptomatic, and was unaccompanied by alteration of the pressure wave form. These findings suggest that instrumentation-related ischemia may occur more often than previously recognized. Persistence of induced regional myocardial dysfunction may indicate the presence of a flow-limiting lesion after angiographically "successful" angioplasty and underscores the limitations of angiography in assessing the physiologic result of angioplasty. Regional wall motion analysis is particularly important in high-risk patients, thus suggesting an important role for TEE in these patients. Decreased venous return as a result of volume depletion or vasodilator therapy does not invariably lead to hypotension because of compensatory tachycardia, but is reflected by decreased LV size as we observed in 2 patients. Thus, continuous assessment of LV volume may prove especially useful in patients with severe LV dysfunction undergoing intervention, since alterations may reflect subtle changes in loading conditions. During balloon inflation, augmented contractility in a region remote to the target vessel was of clinical assistance in 1 patient by demonstration of unexpectedly viable myocardium. The detection of additional findings, such as new mitral regurgitation and the exclusion of pericardial effusion, facilitated immediate diagnosis and management in patients with hemodynamic collapse. Thus, time delays, normally encountered before further intervention, were avoided.

The significance of transiently increased myocardial echogenicity in 4 patients remains unclear. Turbulent coronary flow or atheromatous debris as a result of rotational atherectomy may possibly result in myocardial enhancement; slow myocardial flow after balloon dilation may provide an alternative mechanism.

Left main coronary artery stenosis: Although previous studies have documented the capability of TEE for detecting LMCA stenosis,[10,11] the accurate measurement of stenotic lesion diameter by this method compared with quantitative angiography has not been previously established. In a recent study, Yoshida et al[15] reported that the degree of LMCA stenosis by TEE correlated well with angiography. However, in that study the angiographic interpretation was subjective and not based on quantitative analysis and did not involve patients undergoing LMCA intervention. It could

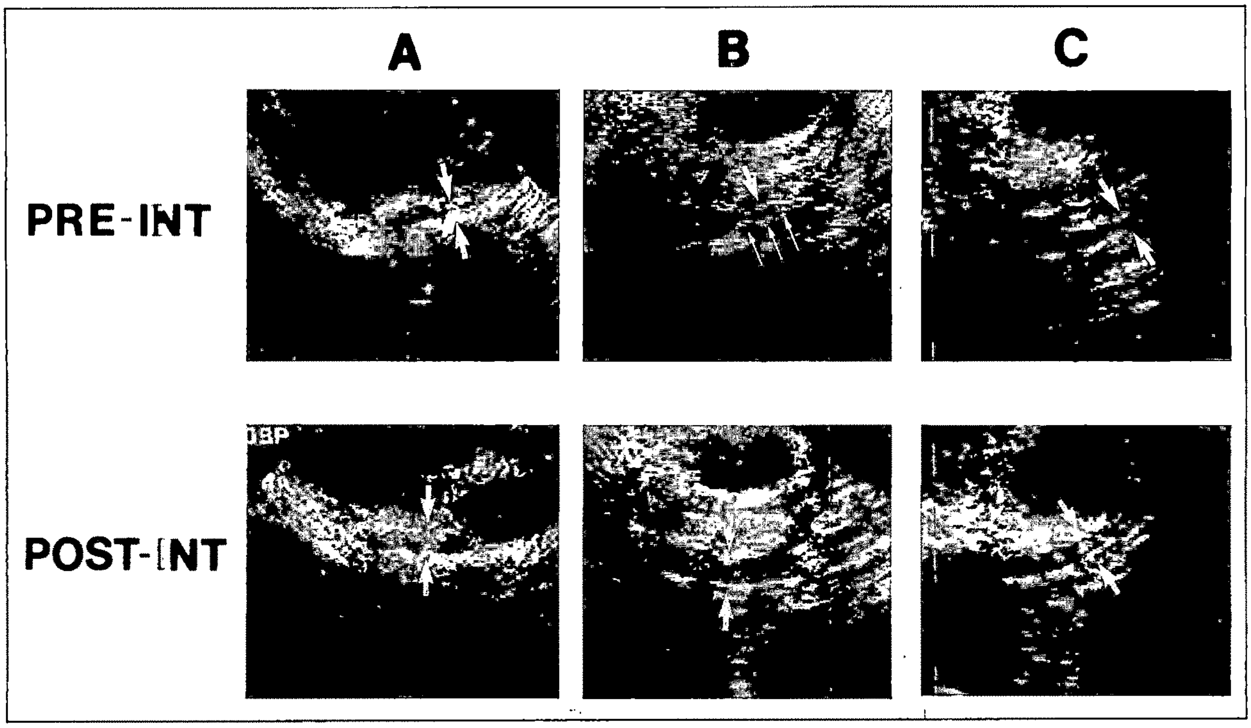

FIGURE 3. Left main coronary artery stenosis before and after intervention (PRE-INT, POST-INT). ***A,*** significant distal left main stenosis before and small residual irregularity after intervention *(arrows)*; ***B,*** eccentric noncalcific left main stenosis before intervention, and widely patent vessel after intervention *(arrows)*; ***C,*** significant distal left main stenosis before intervention, without residual stenosis after intervention *(arrows)* (guidewire still in place).

be argued that in these patients the intraarterial remodeling and intimal disruption make TEE measurements even more difficult. This was not the case in this series because TEE measurements after intervention correlated well with quantitative angiography. The accuracy of TEE measurement, especially after intervention, offers an additional means of follow-up in this subset of patients who have high restenosis rates.

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Effects of Cardiac Denervation on Atrioventricular Nodal Accommodation and Hysteresis

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Conduction through the atrioventricular (AV) node is significantly altered by changes in autonomic tone. AV nodal accommodation (time-dependent changes in AV nodal conduction after a sudden change in atrial cycle length) and AV nodal hysteresis (asymmetry of AV nodal accommodation after directionally opposite atrial pacing cycle length changes) have been characterized in humans. Studies in dogs after cardiac transplantation suggest that the rapid phase of AV nodal accommodation is altered following ablation of neural input to the AV node. To determine if cardiac denervation alters AV nodal accommodation and hysteresis in humans, 13 patients after orthotopic cardiac transplantation and 12 control patients with normal AV nodal function were studied. Atrial pacing was performed for 1 minute at different pacing cycle lengths and AH or AV intervals were measured after cycle length changes.

The rapid phase of accommodation is defined as the time required for the AV interval to reach 75% of the final AV interval. During abrupt changes from long to short pacing cycle lengths, the rapid phase of accommodation took 3.2 ± 1.0 and 4.3 ± 1.0 beats in control subjects and transplant patients, respectively (p = not significant [NS]). When going from short to long pacing cycle lengths, the rapid phase of accommodation took 1.7 ± 1.2 and 2.1 ± 1.8 beats in control subjects and transplant patients, respectively (p = NS). Hysteresis of 1.5 ± 1.3 and 2.1 ± 1.4 beats was noted in the control and transplant groups, respectively (p = NS).

Transplant patients and control subjects behaved in a similar fashion during changes in atrial pacing cycle length, suggesting that neural influences at rest do not play a major role in determining AV nodal accommodation and hysteresis.

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Atrioventricular (AV) nodal accommodation is the adaptation of AV nodal conduction after an abrupt change in atrial pacing cycle length. The AV nodal response to alterations in pacing cycle length is biphasic with most of the final AV interval change occurring within the first several beats.[1-5] This early response is termed the rapid phase of accommodation and may be defined as the time required to achieve 75% of the final AV interval. The slow phase of accommodation follows and is responsible for the last 25% of the final AV interval change. The rapid phase of AV nodal accommodation responds differently to asymmetric changes in pacing cycle length.[6,7] This difference in response is termed hysteresis and is present in both animals and humans. Several investigators have demonstrated that AV nodal conduction is mediated by sympathetic and parasympathetic input, but the effect of autonomic input on AV node accommodation has not been well characterized in humans.

Tuna et al[8] studied AV nodal accommodation and hysteresis in dogs after cardiac transplantation. After cardiac denervation, the rapid phase of AV nodal accommodation is altered and no hysteresis was observed. Based on these findings, the investigators suggested that hysteresis (and the rapid phase of AV nodal accommodation) results primarily from extrinsic (neural) modification of AV nodal conduction.[8]

In humans, initial observations of AV nodal accommodation have been made after sudden changes in atrial rate, but did not include systematic evaluation of accommodation using identical protocols to those used in animal studies.[9-11] We prospectively studied human AV nodal accommodation during symmetric (and opposite) atrial pacing cycle length changes in a control group of subjects referred for electrophysiology study and a group of patients after orthotopic cardiac transplantation. We sought to describe accommodation and hysteresis following orthotopic cardiac transplantation

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and compare that with control subjects undergoing the same pacing protocol.

METHODS

Two groups of male patients were prospectively studied after informed written consent was obtained. The protocol was approved by the institutional review boards of the McGuire Veterans Administration Medical Center and the Medical College of Virginia. All cardiac medications that affect sinus node or AV nodal conduction (e.g., digoxin, β blockers, calcium antagonists, and type 1a antiarrhythmic drugs) were discontinued for at least 4 to 5 half-lives before the study.

The control group consisted of 12 men (mean age 54 ± 9 years [range 36 to 69]) referred for electrophysiologic study to evaluate documented or suspected cardiac arrhythmias. All patients were in normal sinus rhythm and had no evidence of sinus or AV nodal disease during electrophysiologic testing. Three patients had no structural heart disease, and 7 patients had angiographically documented coronary artery disease.

The second group consisted of 13 patients (mean age 50 ± 8 years [range 34 to 61]) who were studied 1 to 84 months (mean 33 ± 10) after orthotopic cardiac transplantation. Thirteen patients were taking cyclosporin A, 11 patients were taking azathioprine and 4 patients were taking prednisone. Seven patients were taking furosemide and most were treated with angiotensin-converting enzyme inhibitors for hypertension. Ten patients had a normal 12-lead electrocardiogram with normal PR, QRS and QT intervals, and 3 patients had a QRS interval of 120 ms. Cardiac transplant patients were studied in the resting supine state 15 minutes after endomyocardial biopsy.

Electrophysiologic study: Studies were performed in the fasting, nonsedated state in all patients. In the control patients, 2 or 3 quadripolar catheters were introduced through the right femoral vein and positioned in the right atrial appendage, across the tricuspid valve to record a His bundle, and in the right ventricular apex. In the cardiac transplant patients, a hexapolar catheter was advanced from the right internal jugular vein to the right atrium where a donor atrial electrogram and far-field ventricular electrogram were recorded. Intracardiac electrograms were filtered at 30 to 500 Hz and simultaneously displayed with 3 surface electrocardiographic leads on a multichannel recorder (Electronics for Medicine, VR-16, Pleasantville, New York). Pacing was performed at twice diastolic threshold (<2 mA) (pulse width of 2 ms) with a custom made, programmable stimulator (Bloom Associates DTU-201, Philadelphia, Pennsylvania) that allowed instantaneous changes in atrial pacing cycle length.

In each group, atrial pacing was performed in stepwise fashion by decreasing the atrial pacing cycle length 10 to 20 ms until the minimal atrial cycle length permitting 1:1 AV conduction was determined (Wenckebach cycle length). We then determined the shortest cycle length during which 1:1 AV conduction occurred with a 1-step protocol. Pacing was then performed for 1 minute at an atrial cycle length 20 ms below the spontaneous sinus cycle length and then immediately changed to an atrial pacing cycle length >40 ms longer than the Wenckebach cycle length. After 1 minute of atrial pacing at the shorter cycle length, the atrial pacing cycle length was then rapidly switched to the original (longer) atrial pacing cycle length. The total change in AV interval was measured and the time interval (and number of beats) required to achieve 75% of the final AV interval was measured, and designated the rapid phase of accommodation. Hysteresis was measured as the difference in the number of beats (and time) between accommodation in 1 direction and accommodation in the opposite direction. AV nodal conduction was measured continuously by recording the AH or AV interval, or both, in control patients and the AV interval in transplant patients. In control (n = 12) and transplant (n = 2) patients where AH and AV intervals were simultaneously measured, AH intervals paralleled AV intervals. AH and AV intervals were recorded at a paper speed of 100 mm/s and measurable to ± 5 ms. AH or AV intervals, or both, were measured during the 10 seconds before rapid change. To be considered stable the measured intervals did not vary by >5 ms.

TABLE I Baseline Clinical and Electrocardiographic Characteristics of Both Groups

	Control	Transplant	p Value
Age (years)	53 ± 9	50 ± 8	0.37
PR (ms)	165 ± 26	155 ± 34	0.41
QRS (ms)	99 ± 12	107 ± 12	0.12
QTc (ms)	427 ± 20	446 ± 21	0.04
Wenckebach CL	380 ± 37	358 ± 70	0.36
Short pacing CL	435 ± 44	415 ± 62	0.36
Long pacing CL	679 ± 96	634 ± 98	0.29
Difference*	55 ± 38	57 ± 36	0.94

*Difference = Wenckebach and short pacing cycle lengths.
CL = cycle length.

Definitions: ATRIOVENTRICULAR NODAL ACCOMMODATION: The time-dependent change in AV nodal conduction after a sudden change in atrial cycle length.

RAPID PHASE OF ACCOMMODATION: The time period required for 75% of the final AV interval to be obtained.

HYSTERESIS: Asymmetry of AV nodal accommodation to rapid changes (in opposite directions) in atrial pacing cycle length.

SHORT PACING CYCLE LENGTH: The shortest cycle length that consistent 1:1 AV conduction could be verified in a 1-step protocol (generally ≥40 ms above Wenckebach cycle length).

LONG PACING CYCLE LENGTH: A pacing cycle 20 to 50 ms faster than the patient's sinus cycle length at rest.

Statistics: Both intragroup and intergroup statistical comparisons were performed. Statistical comparison of the AV nodal response in each group to symmetric pacing cycle length changes (short versus long pacing cycle length) was performed with paired *t* testing using the Bonferonni correction for multiple comparisons. A corrected p value <0.05 was considered significant.

Intergroup comparison (transplant versus control) of AV nodal response to either short pacing or long pacing cycle lengths was performed using unpaired *t* testing. Because accommodation occurred over several beats (not a singular discrete value), a second comparison of the 2 groups (transplant and control) was done by generating a function describing the accommodation curve versus time for both the transplant and control group.

RESULTS

The baseline clinical and electrocardiographic characteristics of the transplant and control groups are listed in Table I. There were no statistical differences between the 2 groups except for QTc at baseline.

The control group consisted of 12 patients. The mean pacing short cycle length was 435 ± 45 ms (range: 380 to 500) and the mean long pacing cycle length was 679 ± 107 ms (range: 500 to 800). The number of beats for accommodation from long to short pacing cycle length was 3.2 ± 1.7 beats. The number of beats required for accommodation from short to long pacing cycle length was 1.7 ± 1.2. Hysteresis (the difference) occurred over 1.5 ± 1.3 beats.

The transplant group consisted of 13 patients. The mean pacing short cycle length was 415 ± 63 ms (range 350 to 600) and the mean long pacing cycle length was 634 ± 99 ms (range 550 to 800). AV nodal accommodation from long to short cycle length occurred with 4.3 ± 1.8 beats. Accommodation from short to long cycle length required 2.1 ± 1.8 beats. Hysteresis occurred over 2.1 ± 1.4 beats. The time course of accommodation from short to long and long to short cycle lengths are shown in Figures 1 and 2.

The p value for intragroup accommodation (short to long versus long to short cycle lengths) was $p < 0.0015$ for control (1.7 ± 1.2 vs 3.2 ± 1.7 beats) and $p < 0.0001$ for transplant (2.1 ± 1.8 vs 4.3 ± 1.8 beats) demonstrating that hysteresis occurred in both the transplant and control groups. The intergroup comparison by unpaired *t* testing and curve fitting showed no significant differences in hysteresis (2.1 ± 1.4 vs 1.5 ±

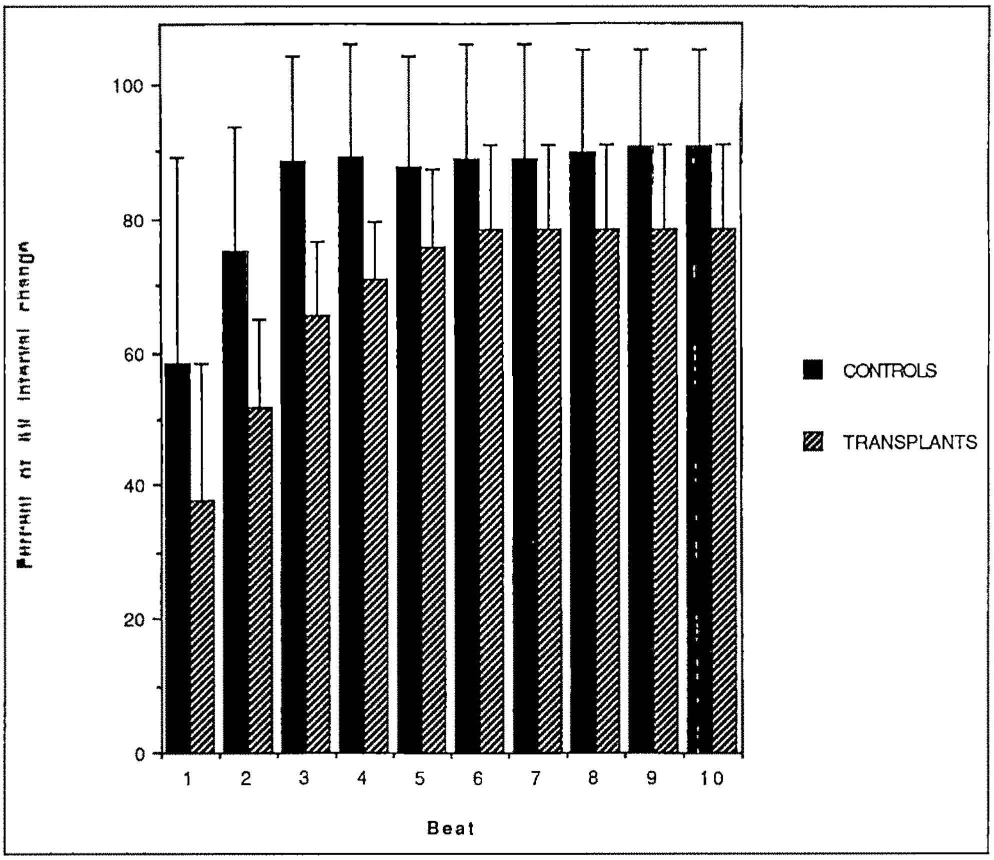

FIGURE 1. Graph showing mean (± standard deviation) percent change in atrioventricular (AV) interval from baseline for the first 10 beats in control *(solid bars)* and transplant *(hatched bars)* patients during short to long atrial pacing cycle length changes. The rapid phase of accommodation is defined as the AV interval that is 75% of the final AV interval.

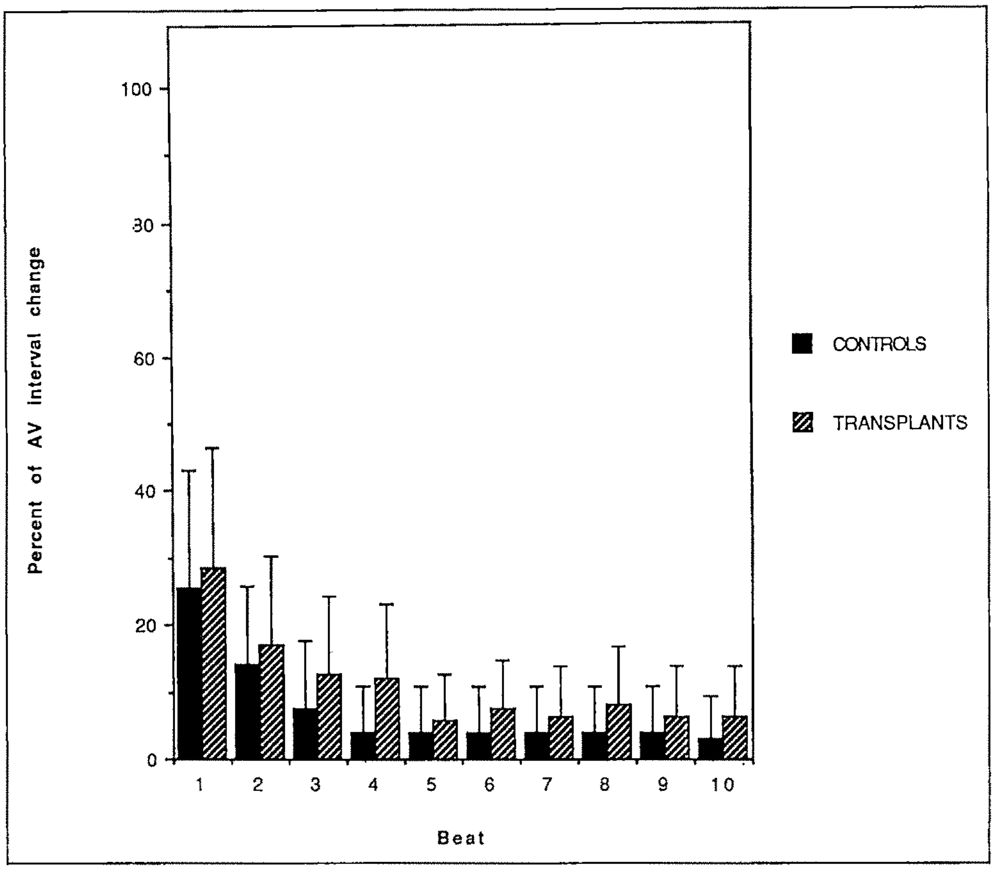

FIGURE 2. Graph showing mean (± standard deviation) percent change in atrioventricular (AV) interval for the first 10 beats in control *(solid bars)* and transplant *(hatched bars)* patients during long to short atrial pacing cycle length changes.

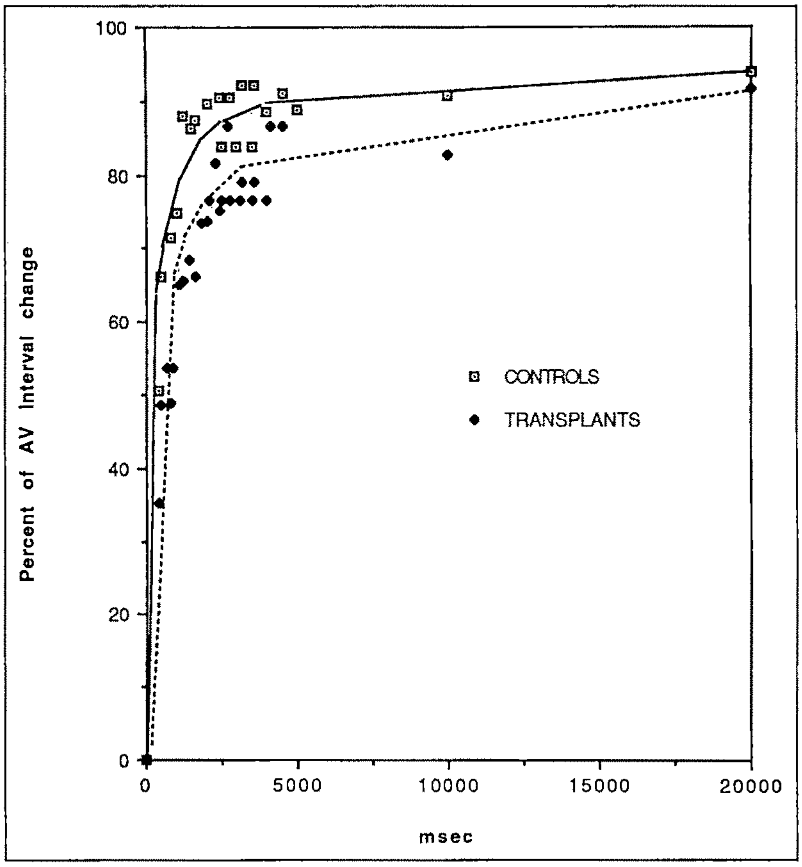

FIGURE 3. Curves showing time course for mean percent change in atrioventricular (AV) interval for all patients during long to short atrial pacing cycle length changes. Control patients, *solid line and squares*; transplant patients, *dotted line and diamonds.* Both rapid and slow phases of AV nodal accommodation are seen in both patient groups.

1.3 beats) or accommodation between transplant and control patients.

Figures 3 and 4 are graphs of the average AV interval for the entire minute after a change (either long to short or short to long) in pacing cycle length for both control and transplant patients.

Blood pressure did not change by >10 to 15 mm Hg (as measured by sphygmomanometer or arterial line) during and after shifts from long to short or short to long cycle lengths. Respiration was not controlled, but there were no changes in the rate of respiration during each pacing protocol.

DISCUSSION

This study prospectively evaluated AV nodal accommodation and hysteresis in control patients and patients after orthotopic cardiac transplantation. The principal observation is that AV nodal accommodation is still present after orthotopic cardiac transplantation and is quantitatively and qualitatively similar to that measured in control patients. A secondary observation is that hysteresis does occur in transplant patients, unlike transplanted dogs where hysteresis is absent.

AV nodal accommodation and hysteresis have been addressed in several studies; however, because of the many factors that affect accommodation, results are often discrepant. Under different initial conditions, accommodation is manifested differently to symmetric changes in pacing cycle length (i.e., short to long versus long to short pacing cycle lengths) affecting both the magnitude and direction of hysteresis. These results highlight the importance of studies showing AV nodal accommodation depends on the previous pacing rate and direction, as well as the final pacing cycle length.[2] This effect has been termed AV nodal memory to help explain cumulative effects of pacing on AV nodal conduction.[11] Therefore, comparisons of results from different studies are likely to be confusing because of differences in pacing protocols.

Systematic characterization of human AV nodal accommodation is difficult because changes in heart rate are also associated with changes in autonomic tone, which secondarily affect AV nodal conduction and thus accommodation.[12] By studying cardiac transplant patients, AV nodal responses independent of autonomic (extrinsic) neural mediation can be characterized and compared with control patients undergoing the same pacing protocol. AV nodal accommodation and hysteresis have not been previously studied and characterized in human cardiac transplant patients.

Accommodation time course and atrioventricular nodal response: During rapid changes in pacing cycle

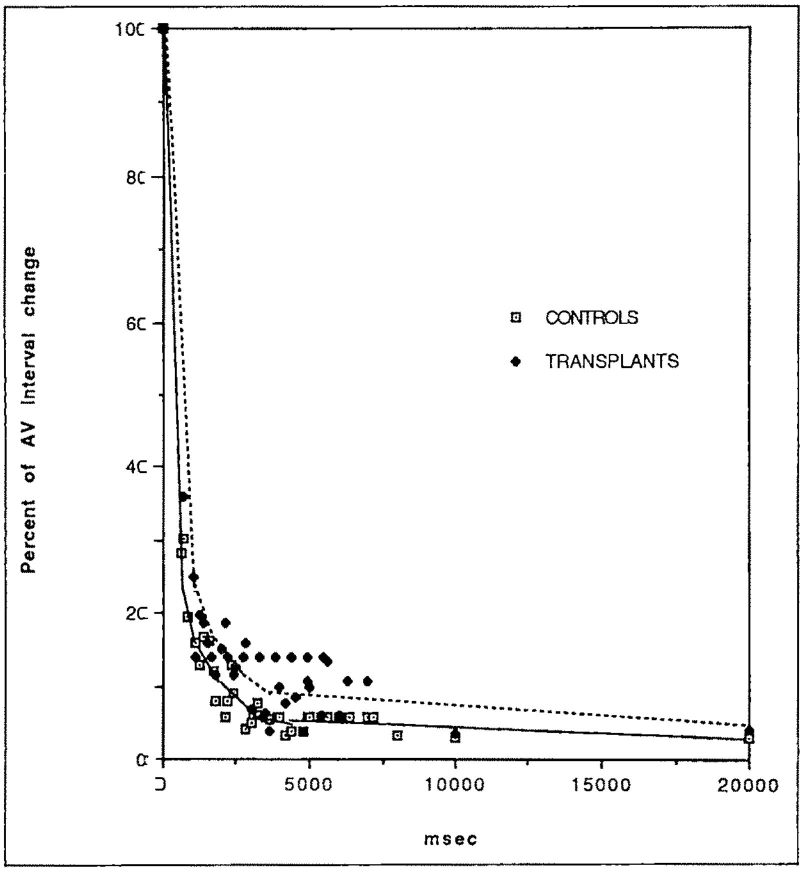

FIGURE 4. Curves showing time course for mean percent change in atrioventricular (AV) interval for all patients during short to long atrial pacing cycle length changes. Control patients, *solid line and squares;* transplant patients, *dotted lines and diamonds.*

length, AV nodal accommodation exhibits a biphasic response, with most of AV nodal accommodation occurring within 10 seconds and the rest occurring over the subsequent 40 to 50 seconds. We observed this biphasic response in both transplant and control patients (Figure 4). The rapid phase of accommodation involved a change in the AV or AH interval of 70 to 80 ms over 1 to 10 seconds, whereas the slow phase of accommodation typically involved a gradual change in AV or AH interval of 10 to 15 ms over 50 seconds. This observation is consistent with previous in vivo and isolated AV node studies as well as computer-generated models of AV nodal behavior.[5,13-16]

Hysteresis after cardiac transplantation: We continued to observe hysteresis after cardiac transplantation, which was qualitatively and quantitatively similar to that seen in control patients.

Many studies of AV nodal accommodation do not address the nonequivalence of AV nodal accommodation systematically. We choose a rapid single step as a reproducible pacing protocol, which is directly comparable to other studies.[8] We continued pacing for 1 minute at the new rate to determine if fatigue was present. It is clear that there is both a time- and rate-dependent effect of pacing on AV nodal conduction and accommodation. We paced for 1 minute at each cycle length because it provided adequate time to observe the long phase of AV nodal accommodation and permitted stable AV conduction. We paced $\geq$40 ms above the Wenckebach cycle length to avoid confusion with long Wenckebach periodicity, and at a rate at which stable 1:1 conduction could repetitively be reproduced.

Tuna et al[8] used a pacing protocol similar to ours in their study of AV nodal accommodation in dogs after heart transplantation. In their study, the rapid phase of AV nodal accommodation was absent and hysteresis was no longer present after cardiac denervation. They suggested the rapid phase of AV nodal accommodation and hysteresis was a result of extrinsic (neural) modification of the AV conduction. Our results in humans differ because both rapid accommodation and hysteresis occur in transplant patients, and suggest that neural mediation is not required for either the rapid phase of accommodation or hysteresis.

The finding of hysteresis in the denervated human AV node suggests that hysteresis may be an intrinsic property of the AV node. Hysteresis has been documented to occur in ventricular myocardium and in single cells during current pulse application. For example, the current needed to stimulate ventricular myocytes is different depending on whether the heart rate is increasing or decreasing. The potential cellular basis for these findings may be related to the slow inward current, responsible for repolarization, which has a slow time constant for recovery from inactivation. In experimental models, the time constant for recovery of the slow potassium current varies in response to the rate of stimulation.[17] Difference in the size and other characteristics of the canine and human AV node may explain the discrepancy between our findings in the human AV node and those reported by Tuna et al. In addition, the need for extensive surgical procedures in dogs necessary to make measurements of AV nodal conduction times may have altered Tuna's results.

Our protocol did not test independence of the atrial pacing site specifically, but there were no differences noted with pacing from the high lateral right atrium, the low right atrium or other atrial sites. In patients with QRS duration $<$120 ms, changes in AH interval should be accurately reflected by changes in AV interval. We did verify that AH and AV intervals were similar in 2 transplant and all control patients. During pacing we did not observe blood pressure changes of $>$10 mm Hg with cycle length changes.

We have shown that transplant and control patients demonstrate similar patterns of AV nodal accommodation after rapid pacing cycle length changes. Therefore, we speculate that the pattern of AV nodal accommodation seen at the onset of supraventricular tachycardia should be remarkably similar in control and transplant patients. Our study demonstrates that in humans the rapid phase of AV nodal accommodation and hysteresis is present after orthotopic cardiac transplantation.

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Initial Blood Pressure Response to Enalapril in Hospitalized Patients (Studies of Left Ventricular Dysfunction [SOLVD])

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William J. Rogers, MD, Donna Howe, RN, Koon K. Teo, MB, PhD, and Thierry H. LeJemtel, MD,
for the SOLVD Investigators

Studies of Left Ventricular Dysfunction (SOLVD) is a randomized trial of enalapril versus placebo in reducing mortality in patients with cardiac dysfunction (defined as left ventricular ejection fraction ≤35%). Before randomization, patients at risk for hypotension were hospitalized for a test dose of 2.5 mg of enalapril administered orally at baseline and again 12 hours later. As of February 1989, 89 of 7,539 (1.2%) patients had been studied during hospitalization. Baseline systolic and diastolic blood pressures were 115 ± 18 and 73 ± 10 mm Hg, respectively. After enalapril, systolic blood pressure decreased slightly but significantly 8 to 20 hours after the initial dose (mean reduction 8 to 11 mm Hg). In this highly selected group of 89 patients, symptoms relating to decrease in blood pressure were noted in 13 (15%). It is emphasized that most patients with cardiac dysfunction readily tolerate enalapril. However, the agent should be administered with caution to patients with advanced congestive failure and diminished baseline blood pressure, owing to a significant incidence of symptomatic hypotension.

(Am J Cardiol 1991;68:1465–1468)

Management of patients with chronic congestive heart failure is a difficult problem. In recent years, conventional management with digitalis and diuretics has been augmented by the use of vasodilators that improve cardiac performance by unloading the heart. Angiotensin-converting enzyme inhibitors are particularly effective. These agents produce acute improvement in hemodynamics,[1,2] as well as long-term improvement in exercise tolerance and symptoms.[3,4]

The role of angiotensin-converting enzyme inhibitors in prolonging life in patients with congestive heart failure is also of great importance. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) showed that converting enzyme inhibitors could prolong life in patients with New York Heart Association class IV cardiac failure.[5] However, the effects in patients with mild to moderate congestive failure were unknown. For this reason, a large-scale National Heart, Lung, and Blood Institute-sponsored randomized trial of the angiotensin-converting enzyme inhibitor enalapril has been conducted to determine whether long-term therapy reduces mortality. The trial is referred to as SOLVD (Studies of Left Ventricular Dysfunction). The results of the Treatment Trial arm of SOLVD in patients with overt congestive failure (mostly New York Heart Association classes II and III) have recently been published and show that mortality is reduced in this group also.[6]

Although the incidence of side effects with angiotensin-converting enzyme inhibitors is considered to be low, hypotension, renal dysfunction, skin rashes and angioneurotic edema, cough, leukopenia and taste disturbances have been described.[7-12] The hypotensive response to initial administration of angiotensin-converting enzyme inhibitors is well documented,[13] and there was particular concern that patients with more severe cardiac dysfunction might experience this side effect.[14,15] Accordingly, the SOLVD investigators designed the study to include test doses of enalapril in all patients. Investigators had the option of hospitalizing patients who were thought to be potentially vulnerable

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TABLE I Baseline Characteristics

	Hospitalized Patients (n = 89)	Nonhospitalized Patients	
		Qualifying (n = 2,905)	Nonqualifying (n = 4,545)
Age (yrs)	60.3 ± 11.8	60.1 ± 9.9	59.7 ± 10.5
Men/women ratio	2.9*†	5.8	5.9
Vasodilator, nonan ACE inhibitor or nitrate (%)	66.2*†	96.1†	0.0
Diuretics (%)	62.9*†	39.8†	37.5
Serum sodium (mEq/L)	138.6 ± 4.0*†	139.8 ± 3.1†	140.1 ± 3.0
Systolic pressure (mm Hg)	114.4 ± 16.1*†	125.9 ± 17.5	125.3 ± 17.6
Diastolic pressure (mm Hg)	72.7 ± 10.1*†	77.5 ± 10.5†	78.3 ± 10.3
Heart rate (beats/min)	84.7 ± 15.0*†	74.4 ± 12.8†	77.0 ± 13.2
Ejection fraction (%)	22.1 ± 7.6*†	27.6 ± 6.0†	26.9 ± 7.3
Heart failure score‡	2*†(2.23)	1 (0.89)	1 (0.86)
NYHA class I (%)§	10	49	52
NYHA class II (%)	24	40	37
NYHA class III (%)	40	10	9
NYHA class IV (%)	26	1	0

*$p < 0.05$ compared with nonhospitalized qualifying patients; †$p < 0.05$ compared with nonhospitalized nonqualifying patients.

‡Value shown for heart failure score is median with mean in parentheses.

§Distribution of NYHA class tested among the 3 groups using the Mantel-Haenszel chi-square test; results significantly different at $p < 0.05$ for hospitalized patients compared with nonhospitalized qualifying and nonqualifying patients.

Among nonhospitalized patients, "qualifying" refers to presence and "nonqualifying" to absence of NYHA class IV status, non-ACE inhibitor or non-nitrate vasodilator therapy, or serum sodium <130 mEq/liter.

ACE = angiotensin-converting enzyme; NYHA = New York Heart Association.

to hypotension for observation during the test doses. This report presents the results of the test doses of enalapril in these hospitalized patients.

METHODS

SOLVD includes patients with left ventricular ejection fractions $\leq 35\%$ who are New York Heart Association class I to IV. The study began in June 1986, with a planned duration of 5 years. No patient was admitted to the hospital for monitoring after February 28, 1989. As of that date, 7,539 patients had been seen for an initial visit. The study design called for the administration of 2 test doses of enalapril at this initial visit. Patients who experienced intolerable side effects would therefore be excluded from the randomization. Suggested criteria for admitting patients to hospital for observation were history of New York Heart Association class IV cardiac failure, treatment with a nonangiotensin-converting enzyme inhibitor vasodilator other than nitrates, and serum sodium <130 mEq/liter. The purpose of hospitalizing these patients who were potentially at increased risk for hypotension was to gain experience with drug safety. Admission was not mandatory if the patient displayed the suggested criteria. A patient could also be admitted based on the investigator's concern even if the patient did not meet the criteria.

After admission to the hospital, an initial test dose of 2.5 mg of enalapril was administered orally, followed by a second 2.5 mg dose 12 hours later. Cuff blood pressure was recorded in the supine position at intervals after the test doses. Side effects including dizziness and syncope were recorded. At the end of the study period patients were discharged from the hospital. Baseline characteristics and blood pressure responses in symptomatic hospitalized patients were tested against those in nonhospitalized patients using Student's *t*, Mantel-Haenszel or Pearson chi-square test, as appropriate. Changes in blood pressure for all patients across all measured points in time were tested for significance using a repeated measures analysis of variance, and pairwise time comparisons were obtained with paired Student's *t* tests using the Bonferroni correction. Potential risk factors for development of symptoms were tested by univariate logistic regression. Data are represented as mean ± standard deviation. For clinical symptoms and signs, a "heart failure score" was calculated based on a modification of the method of Lee et al.[16] One point was assigned for each of the following: breathlessness on exertion, pulmonary rales, S3 gallop, increased jugular venous pressure, peripheral edema, heart rate >100 beats/min and presence of pulmonary congestion on chest x-ray (maximal number of points = 7). The Wilcoxon signed-rank test was used to test the significance of score differences between groups.

RESULTS

Of 7,539 patients administered test doses of enalapril at the initial visit, 89 (1.2%) were admitted to the hospital. An additional 2,905 patients (39%) were New York Heart Association class IV or on nonangiotensin-converting enzyme inhibitor nonnitrate vasodilators, or had serum sodium <130 mEq/liter, but were not hospitalized by the investigators for the test dose of enalapril. Patient characteristics are listed in Table I. The 89 hospitalized patients had a more advanced degree of congestive failure, as judged by New York Heart Association class, than did the 2,905 who met the suggested criteria, but were not hospitalized. They also had greater use of diuretics, and lower serum sodium, systolic and diastolic blood pressures, and left ventricular ejection fraction, and higher heart rate and heart failure score. Nonhospitalized patients who met the suggested criteria for hospitalization also differed from those who did not in greater use of diuretics, and lower serum sodium, diastolic pressure and heart rate, and a slightly but significantly higher ejection fraction (Table I).

Results of monitoring blood pressure after administration of test doses of enalapril are listed in Table II. Repeated measures analysis of variance showed a significant difference from baseline over total time of observation for both systolic ($p < 0.007$) and diastolic ($p < 0.02$) pressures. Pairwise comparisons showed that systolic pressure was significantly lower than baseline for hours 8 to 20, and diastolic pressure for hours 16 to 24. Dizziness developed in 11 patients, and 2 had syncope during the course of the study. A series of univariate logistic regression models were tested to evaluate factors that might predispose patients to these symptoms. Factors evaluated were age, New York Heart Association class, vasodilators, diuretics, serum sodium, systolic pressure and left ventricular ejection fraction. None of the risk estimates were significant at the 0.05 level. However, in a subset of patients with baseline systolic pressure <100 mm Hg, 5 of 12 (42%) became symptomatic during the study compared with 8 of 77 (10%) with systolic pressure ≥100 mm Hg (chi-square = 5.83; $p = 0.016$). In the 11 patients that developed dizziness, systolic blood pressure decreased from 112 ± 11 at baseline to 98 ± 13 mm Hg during the episode of dizziness, and diastolic pressure decreased from 71 ± 7 to 61 ± 12 mm Hg. In the 2 patients that developed syncope, the pressures decreased from 96/60 to 80/55 and from 96/60 to 74/42 mm Hg at baseline and during syncope, respectively.

TABLE II Blood Pressure Responses to Enalapril (mm Hg)

Time (hr)	n*	Systolic	Diastolic
Baseline†	89	115 ± 18	73 ± 10
1	80	−2 ± 10	−2 ± 9
2	81	−4 ± 15	−3 ± 10
3	77	−5 ± 14	−5 ± 9
4	82	−6 ± 14	−6 ± 10
8	76	−8 ± 15‡	−6 ± 10
12	77	−8 ± 16‡	−6 ± 13
16	74	−10 ± 15‡	−7 ± 12‡
20	68	−11 ± 16‡	−6 ± 12‡
24	61	−6 ± 16	−5 ± 12‡

*Number of observations at each time point; statistics performed in subset of patients with complete data at all time points (n = 52).

†Baseline data are actual pressures; all other data are changes in pressure.

‡$p < 0.05$ compared with control subjects.

DISCUSSION

The activity of the renin-angiotensin-aldosterone system depends on the clinical status of patients with congestive heart failure.[17] The system becomes activated when cardiac output and systemic arterial pressure are reduced owing to myocardial damage. When new myocardial damage supervenes, or compensatory hypertrophy fails, ventricular performance decreases while arterial impedance is increasing, cardiac output and arterial pressure continue to decrease, and the renin-angiotensin-aldosterone system is further activated. Hemodynamic and clinical benefits of angiotensin-converting enzyme inhibition have, for the most part, been demonstrated in the decompensated stage of congestive heart failure.[18,19]

Angiotensin-converting enzyme inhibitors have been well-tolerated in most clinical studies.[3,4,7-12] Nonetheless, the SOLVD investigators were given the opportunity to hospitalize patients thought to be at risk for hypotension during test doses of enalapril. The 89 patients hospitalized for observation were more severely ill than those not hospitalized, as shown by a more advanced New York Heart Association class, and lower serum sodium, blood pressure and ejection fraction, and higher heart rate and heart failure score (Table I). After the initial 2.5 mg dose of enalapril, a significant reduction in blood pressure was evident by the eighth hour, which persisted up to the 12th hour when the second 2.5 mg dose of enalapril was administered, through to the twenty-fourth hour when the study was terminated (Table II). Symptoms of dizziness or syncope occurred in 13 of these patients (15%) and were associated with a more substantial reduction in blood pressure than for the group as a whole. There was considerable heterogeneity in the baseline characteristics of the patients that developed symptoms, and age, New York Heart Association class, vasodilators, diuretics, serum sodium, systolic pressure, and left ventricular ejection fraction did not prove to be predictive of symptoms by univariate logistic regression analysis. However, a subset of patients with systolic blood pressure <100 mm Hg was identified who showed a significantly higher incidence of symptomatic hypotension.

It is evident from this investigation that small doses of the angiotensin-converting enzyme inhibitor enalapril are readily tolerated by most patients with cardiac dysfunction thought to be at risk for hypotension. However, patients with relatively advanced congestive failure and with systolic pressure <100 mm Hg appear to be at increased risk for symptomatic hypotension.

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Systemic and Left Ventricular Responses to Exercise Stress in Asymptomatic Patients with Valvular Aortic Stenosis

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Patients with heart disease may have myocardial ischemia or left ventricular (LV) dysfunction without symptoms. The exercise responses of 14 asymptomatic patients with valvular aortic stenosis (AS) were studied using treadmill testing, thallium-201 scintigraphy and radionuclide angiography. Compared with age- and gender-matched control subjects, patients with AS demonstrated reduced exercise tolerance (10.7 ± 2.5 vs 13.3 ± 4.2 min; $p = 0.06$) and maximal oxygen consumption (26.7 ± 6.3 vs 36.3 ± 9.5 ml O_2/min/kg; $p = 0.004$) associated with decreased peak systolic blood pressure response to exercise (177 ± 18 vs 214 ± 42 mm Hg; $p < 0.004$). Ten of 14 patients developed ST-segment depression during exercise, only 3 of whom had reversible thallium defects. Patients with AS tended to have greater LV ejection fractions at rest (65 ± 11 vs 58 ± 7; $p = 0.08$) and significantly decreased early peak filling rates (4.8 ± 1.3 vs 6.1 ± 0.6 stroke volume/s; $p = 0.003$) compared with those of control subjects. During maximal supine exercise, patients with AS had less of an increase in ejection fraction (2 ± 9 vs 15 ± 7%; $p < 0.001$) associated with a decrease in end-diastolic (−7 ± 15 vs +5 ± 16%; $p = 0.06$) and stroke (−6 ± 17 vs +30 ± 13%; $p < 0.001$) volumes from baseline measurements. The limitation in stroke volume and heart rate to exercise stress in patients with AS was associated with attenuation of the cardiac output response during exercise compared with that of control subjects (73 ± 48 vs 284 ± 48%; $p < 0.001$), which correlated directly with effort limitation ($r = 0.717$, $p = 0.004$). Thus, despite the absence of symptoms patients with AS demonstrate limited effort tolerance with abnormal systemic and LV hemodynamics, which is most likely a consequence of the inability to augment end-diastolic volume during exercise.

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In adult patients with valvular aortic stenosis (AS), valve replacement is commonly deferred until symptoms such as effort dyspnea, chest pain and alterations in consciousness are reported to the physician.[1-3] However, patients with AS may have impaired left ventricular (LV) function in the absence of symptoms, because of denial, gradual decrease in activity level, or cardiac or peripheral compensation. Although exercise testing might allow functional and hemodynamic assessment of the asymptomatic patient with significant AS, current guidelines advise against such testing,[4] an approach supported by occasional reports of hemodynamic collapse during exercise of symptomatic patients.[5,6]

Nonetheless, knowledge of a patient's exercise response may support a continued nonoperative approach to the asymptomatic patient or may identify patients at relatively high risk because of abnormal exercise hemodynamics that may then result in recommendation for early valve replacement. Furthermore, an investigator with a large operative experience has recently argued for earlier operative intervention in patients with AS in an attempt to improve long-term postoperative survival.[7] This study assesses exercise capacity, hemodynamics, myocardial perfusion and LV function in patients with AS to determine whether abnormal responses are demonstrable in patients without symptoms.

METHODS

Patients: Fourteen patients with clinical and echocardiographic evidence of valvular AS participated in this study. There were 12 men and 2 women (age range 28 to 65 years, average 42). All patients denied effort limitation or dyspnea, chest discomfort and alterations in consciousness. No patient had underlying pulmonary disease, anemia, peripheral vascular disease, disease of other heart valves, known coronary artery disease or cardiomyopathy. The patients were com-

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TABLE I Patient Characteristics, and Electrocardiographic and Echocardiographic Data

Patient	Age (yr) & Sex	LVH by EKG	Valve Gradient (mm Hg)	LVMI (g/m²)	LVED (cm)
1	35 M	+	144	227	5.4
2	33 M	0	125	136	4.8
3	38 M	+	80	101	4.5
4	62 M	+	80	161	5.5
5	65 M	+	64	142	4.4
6	28 M	0	64	126	5.0
7	55 M	0	64	142	5.7
8	33 M	0	64	114	5.3
9	33 M	0	52	139	4.4
10	35 M	+	49	191	6.7
11	36 M	+	40	153	5.6
12	63 F	0	40	170	5.8
13	32 F	0	40	129	5.6

EKG = electrocardiography; LVED = left ventricular end-diastolic dimension; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; + = presence; 0 = absence.

pared with 2 separate sets of age- and sex-matched control subjects. Control subjects were asymptomatic volunteers and were free of heart disease by history, physical examination and electrocardiogram. The control group for treadmill exercise testing consisted of 12 men and 2 women (average age 46 years, range 30 to 71). The control group for radionuclide angiography consisted of 10 men and 2 women (average age 40 years, range 2[illegible] to 60).

Study protocol: All patients and the control subjects for radionuclide angiography underwent M-mode and 2-dimensional echocardiography with continuous wave Doppler estimate of the aortic valvular gradient, using the modified Bernoulli equation.[8] LV mass was estimated from the M-mode echocardiogram using the American Society of Echocardiography method, modified by Devereux.[9] Written informed consent was obtained from all patients for the performance of noninvasive studies described below.

Treadmill testing: Graded treadmill exercise testing was performed using the standard Bruce protocol, with continuous monitoring of 12-lead electrocardiogram and blood pressure measurement at 1 minute intervals. Intraarterial measurements were obtained in patients, whereas blood pressure was monitored in the control subjects by cuff sphygmomanometry. In all studies, exercise was continued to exhaustion or development of symptoms. Ventilation variables were measured with breath-by-breath analysis of expired gases (SensorMedics Horizons MMC 4400, Anaheim, California), and included the following parameters[10]: VO_2max = maximal oxygen consumption per kilogram during exercise; % predicted VO_2max = percent of predicted maximal oxygen consumption for a group of subjects of the same age, sex, weight and height; and VT = ventilation (anaerobic) threshold from visual inspection of the curves relating minute ventilation to oxygen consumption and carbon dioxide release, and carbon dioxide release to oxygen consumption and time. These determinations were averaged for each subject.

Thallium-201 scintigraphy: Thallium-201 single photon emission computed tomography was performed in 12 of 14 patients with 2 mCi of thallium-201 injected approximately 1 minute prior to the termination of exercise, and with imaging (Apex 415, APC-3 Elscint, Boston, MA) at 10 minutes following exercise and after 3–4 hours of rest. Details of count acquisition and image analysis have been described previously.[11]

Radionuclide ventriculography: Technetium-99m gated blood pool scintigraphy was performed at rest and during symptom-limited graded supine bicycle ergometry. Exercise was performed in 25 watt increments at 2 minute intervals. Peak diastolic filling rates were computed from analysis of time-activity curves, as previously described,[12] and were expressed relative to LV stroke volume. The relative changes during exercise in end-diastolic, end-systolic and stroke volumes, and cardiac output were computed from analysis of changes in counts at appropriate points in the cardiac cycle, comparing rest with peak exercise after correction for physical decay of the isotope. Whereas ejection fraction is measured as a percentage, ejection fraction response was computed as the difference between values during exercise and at rest. Changes in relative LV volumes were computed as a percentage of the resting value.

Statistical analyses: All data are reported as mean ± 1 standard deviation. Group data were compared using 2-tailed Student's *t* test. Linear regression analyses were performed where indicated. A $p < 0.05$ was considered significant.

RESULTS

Echocardiographic and electrocardiographic data (Table I): LV end-diastolic dimensions were slightly larger for patients than for control subjects (5.2 ± 0.7 vs 4.8 ± 0.5 cm), although not statistically significant. The peak instantaneous aortic valve gradients at rest for patients ranged from 40 to 144 mm Hg (mean 68), and the estimated LV mass index ranged from 92 to 227 g/m^2 (mean 145). Ten patients had LV hypertrophy by echocardiography (>134 g/m^2 in men; >110 g/m^2 in women).[9] Seven patients had electrocardiographic evidence of LV hypertrophy using Estes' criteria[13]; the remaining 7 had normal electrocardiograms at rest. There was no correlation between magnitude of aortic valve gradient at rest and LV mass index or presence or absence of LV hypertrophy by electrocardiography.

Treadmill exercise results: Baseline and exercise treadmill hemodynamics are listed in Table II. Baseline heart rate, systolic blood pressure and oxygen consump-

TABLE II Baseline and Treadmill Exercise Hemodynamic and Ventilation Parameters

	Control Subjects	Patients	p Value
Rest			
Heart rate (beats/min)	79 ± 10	73 ± 14	NS
Systolic blood pressure (mm Hg)	136 ± 17	141 ± 18	NS
VO_2 (ml O_2/min/kg)	3.8 ± 0.9	4.6 ± 1.3	NS
End exercise			
Heart rate	177 ± 14	171 ± 19	NS
Systolic blood pressure (mm Hg)	214 ± 42	167 ± 22	<0.001
VO_2max (ml O_2/min/kg)	36.3 ± 9.5	26.7 ± 6.3	0.004
% predicted VO_2max	104 ± 24	75 ± 19	0.002
VT (ml O_2/min/kg)	18.9 ± 4.6	17.5 ± 3.6	NS
Duration (min)	13.3 ± 4.2	10.7 ± 2.5	0.06

max = maximal; NS = not significant; VO_2 = oxygen consumption; VT = ventilation (anaerobic) threshold.

tion did not differ between patients with AS and control subjects. During symptom-limited upright treadmill exercise, 13 of 14 patients stopped because of fatigue. One patient stopped because of light-headedness despite having a systolic blood pressure of 150 mm Hg. All control subjects stopped because of fatigue. Patients demonstrated reduced effort tolerance with a mean exercise time of 10.7 ± 2.5 min compared with 13.3 ± 4.2 min for control subjects, which was of borderline statistical significance ($p = 0.06$). Although heart rate response was similar between the 2 groups, peak systolic blood pressure response was significantly lower in patients than in control subjects (177 ± 18 vs 214 ± 42 mm Hg; $p < 0.004$; Figure 1). One patient had a continuous decrease in systolic blood pressure during exercise (173 to 155 mm Hg), and 1 had a <10 mm Hg increase in systolic blood pressure during exercise (155 to 161 mm Hg). Seven additional patients had a reduction in systolic blood pressure from peak pressure to pressure at the end of exercise (28 mm Hg in 1 patient, and <10 mm Hg in the others). The systolic blood pressure at the end of exercise was 167 ± 22 mm Hg. VO_2max was significantly lower for patients than for control subjects (26.7 ± 6.3 vs 36.3 ± 9.5 ml O_2/min/kg; $p = 0.004$), as was % predicted VO_2max (75 ± 19% vs 104 ± 24%; $p = 0.002$). Ventilatory threshold, an index of anaerobic threshold during exercise, was similar between the 2 groups.

During exercise, 6 of the 7 patients with LV hypertrophy on baseline electrocardiography developed significant ST-segment depression (average 4 mm, range 2 to 5). Of the 7 patients with normal electrocardiograms at rest, 4 developed ST-segment depression with exercise (average 3 mm, range 2 to 5), 1 developed a right bundle branch block, and the remaining 2 patients had no electrocardiographic changes compared with

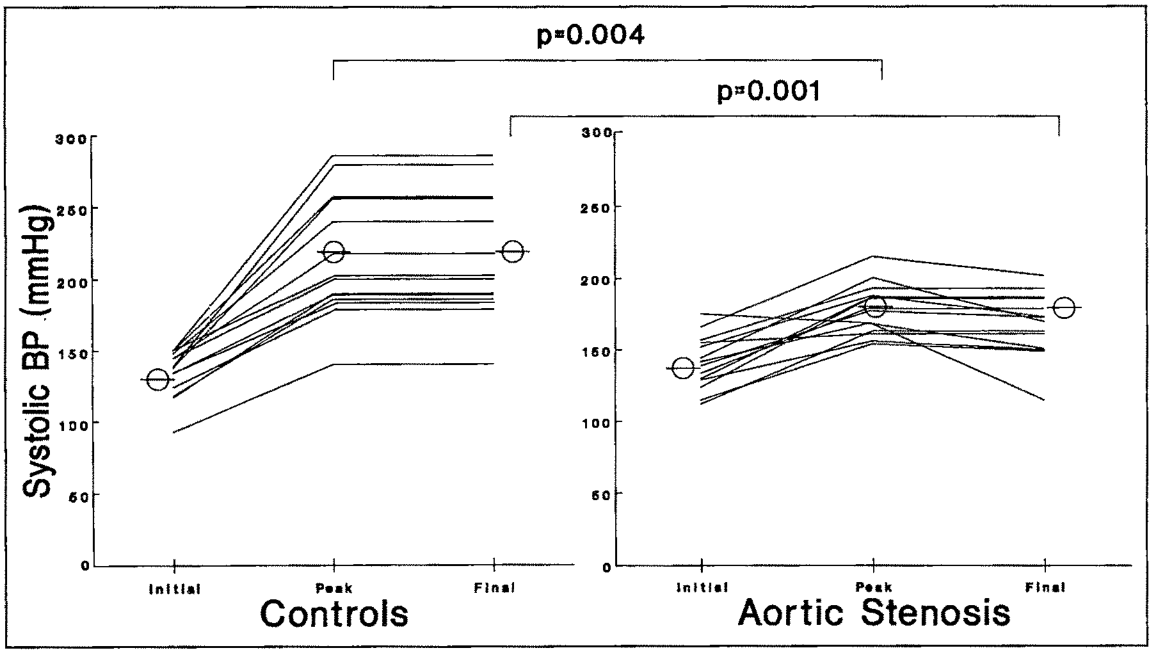

FIGURE 1. Systolic blood pressures (BP) at rest and during graded treadmill exercise (Bruce protocol) are shown for control subjects and asymptomatic patients with aortic stenosis.

TABLE III Rest and Exercise Radionuclide Angiographic Data

	Control Subjects	Patients	p Value
Rest			
Heart rate (beats/min)	66 ± 12	71 ± 12	NS
Systolic blood pressure (mm Hg)	124 ± 13	120 ± 10	NS
LV ejection fraction (%)	58 ± 7	65 ± 11	0.08
Peak filling rate (SV/sec)	6.1 ± 0.6	4.8 ± 1.3	0.003
Peak exercise			
Heart rate	156 ± 16	134 ± 18	0.003
Systolic blood pressure (mm Hg)	198 ± 31	143 ± 12	0.002
Work load (W)	181 ± 28	88 ± 27	<0.001
Duration (min)	13.9 ± 2.4	6.1 ± 2.4	<0.001
LV ejection fraction (%)	73 ± 9	67 ± 15	NS
LV ejection fraction change from baseline (%)	+15 ± 7	+2 ± 9	<0.001
% change from baseline			
LV end-diastolic volume	+5 ± 16	−7 ± 15	0.06
LV end-systolic volume	−30 ± 28	−13 ± 30	NS
Stroke volume	+30 ± 13	−6 ± 17	<0.001
Cardiac output	+284 ± 48	+73 ± 48	<0.001

LV = left ventricular; NS = not significant; SV = stroke volume.

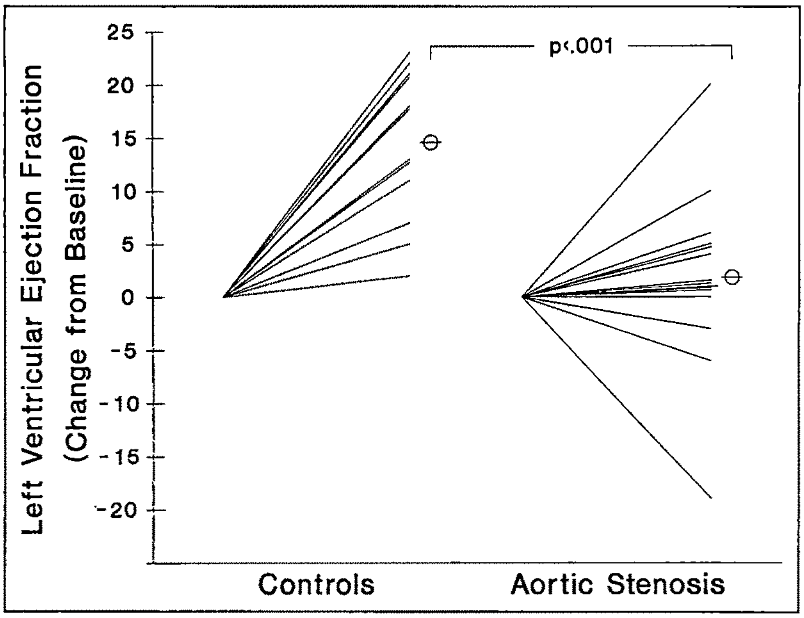

FIGURE 2. Changes in left ventricular ejection fraction from rest to peak supine bicycle exercise are shown for control subjects and patients with aortic stenosis.

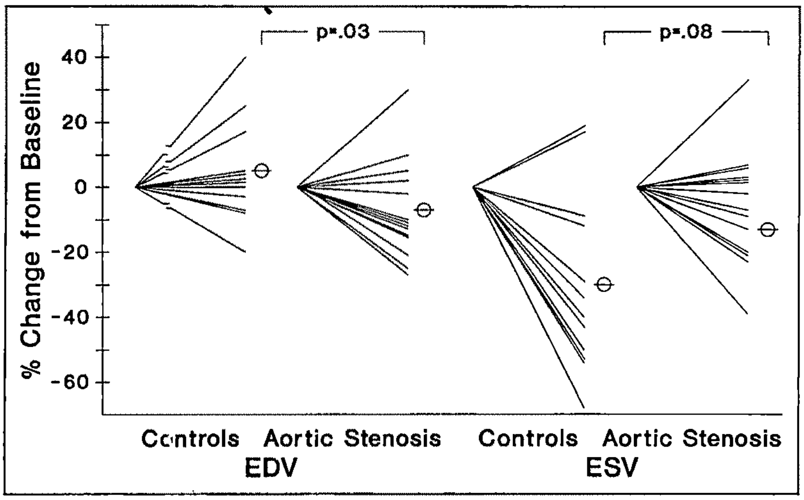

FIGURE 3. Changes in end-diastolic (EDV) and end-systolic (ESV) volumes from rest to peak supine exercise by radionuclide angiography are shown for control subjects and patients with aortic stenosis.

baseline. No control subject demonstrated significant electrocardiographic changes during exercise.

Thallium scintigraphy: Thallium scintigraphy was normal in 9 of the 12 patients in whom studies were performed (including 7 patients with 3 to 5 mm ST-segment depression during exercise), and demonstrated reversible regional perfusion defects in 3. No patient had evidence of endocardial hypoperfusion, as indicated by apparent cavity dilatation after exercise. Of the 3 patients with reversible thallium defects, 1 was a 34-year-old patient without risk factors for coronary artery disease, the second was a 60-year-old man who underwent cardiac catheterization and was found to have angiographically normal coronary arteries, and the third was a 65-year-old man who refused cardiac catheterization. There was no relation between thallium results and exercise performance or electrocardiographic responses. Although all 3 patients with reversible regional thallium defects had >2 mm ST-segment depression during exercise, and 2 had a reduction in LV ejection fraction during exercise, there were 7 others with ST-segment depression and 2 with either a decrease or no change in ejection fraction during exercise who had entirely normal thallium studies.

Radionuclide angiography: As listed in Table III, heart rate and systolic blood pressure at rest, measured during radionuclide angiography, did not differ between the patients and control subjects. LV ejection fraction at rest for patients ranged from 46 to 83% and was slightly but insignificantly higher than for control subjects (65 ± 11 vs 58 ± 7; p = 0.08). Despite higher LV ejection fractions at rest, patients had a significantly reduced peak LV filling rate (4.8 ± 1.3 vs 6.1 ± 0.6 stroke volume/s; p = 0.003). There was an inverse correlation of the peak filling rate with age (r = −0.678, p = 0.008), but not with LV mass index (r = −0.091, p = not significant).

During supine bicycle exercise, patients had a significantly shorter duration of exercise (6.1 ± 2.4 vs 13.9 ± 2.4 min; p <0.001) and lower workload (88 ± 27 vs 181 ± 28 W; p <0.001) at a lower systolic blood pressure (198 ± 31 vs 143 ± 12 mm Hg; p = 0.002) and heart rate (134 ± 18 vs 156 ± 16 beats/min; p = 0.003) than did control subjects. Control subjects responded to exercise with a 15 ± 7% increase in ejection fraction compared with that at baseline, in contrast to an only 2 ± 9% increase in patients (p <0.001; Figure 2). Three patients demonstrated an actual decrease in ejection fraction during exercise, and 1 had no change in ejection fraction compared with that at baseline. The relevance of this abnormal ejection fraction response to exercise is suggested by the lower VO_2max (20.6 ± 2.6 vs 29.1 ± 5.6 ml O_2/min/kg; p = 0.08) and % predicted VO_2 max (61 ± 7 vs 81 ± 19%; p = 0.04) in these 4 patients compared with the 10 whose LV ejection fractions increased during exercise.

The patients also demonstrated a decrease in end-diastolic volume during exercise (−7 ± 15%) compared with an increase in that of control subjects (5 ± 16%; p = 0.06; Figure 3). In contrast to the 30 ± 28% decrease in end-systolic volume with exercise demonstrated by control subjects, patients had a less substantial decrease in end-systolic volume (13 ± 30%), although this did not achieve statistical significance (p = 0.08). As a result, stroke volume decreased during exercise in the patients (−6 ± 17%) and increased in control subjects (30 ± 13%; p <0.001; Figure 4). As shown in Figure 5 there was a similar and significant correlation between the changes in end-diastolic and stroke volumes with exercise for both patients and control subjects. Examination of these relations reveals clustering of the control subjects toward the middle and upper end of this relation, and of the patients toward the lower end, reflecting the significant differences in

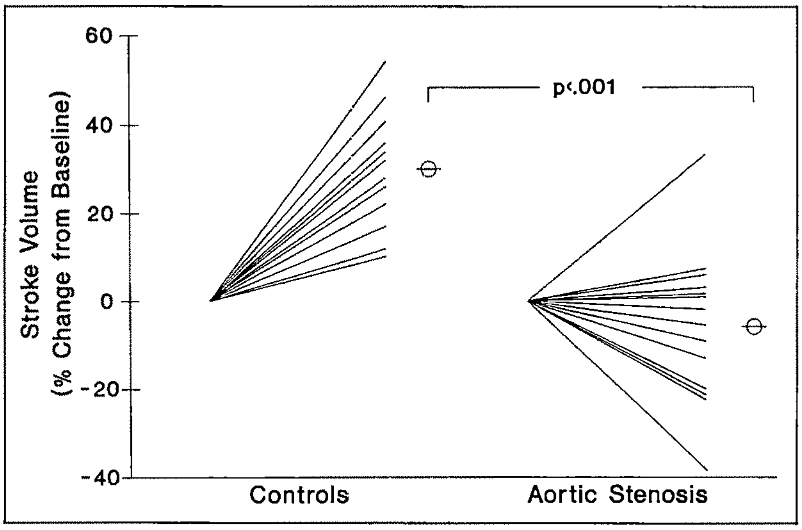

FIGURE 4. Changes in stroke volume from rest to peak supine exercise are shown for control subjects and patients with aortic stenosis.

both stroke and end-diastolic volume responses of these 2 groups during exercise. In contrast, there was no relation between changes in end-systolic and stroke volumes during exercise for either patients (r = 0.06) or control subjects (r = 0.197). The actual decrease in stroke volume during exercise and the lower heart rate response during supine exercise translated into a marked reduction in the cardiac output response to exercise for patients compared with control subjects (73 ± 48 vs 284 ± 48%; p <0.001; Figure 6). As shown in Figure 7, the limitation in cardiac output response to exercise correlated significantly with the limited exercise duration and work load of patients during supine bicycle exercise.

DISCUSSION

Exercise studies have been reported in patients with valvular AS, but largely restricted to young patients with congenital valvular disease.[14-21] Abnormal electrocardiographic (ST-segment depression) and hemodynamic responses (blunted blood pressure response or actual decrease in blood pressure during exercise) have frequently been noted in these patients, even in the absence of symptoms. Aronow and Harris[22] reported that 7 of 19 symptomatic adult patients with AS and angiographically normal coronary arteries had >1 mm ST-segment depression during exercise, but this did not correlate with magnitude of valvular gradient at rest. Areskog[6] reported a reduction in blood pressure during

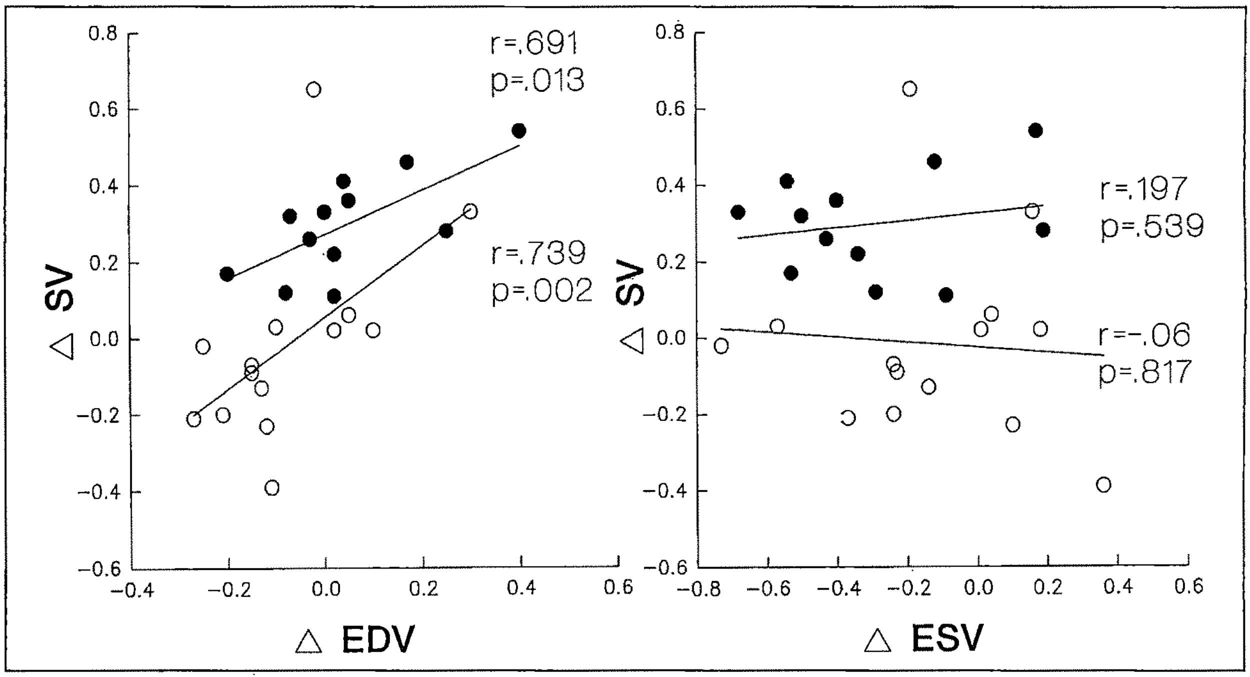

FIGURE 5. Changes in stroke volume (Δ SV) from rest to peak supine exercise plotted in relation to changes in end-diastolic (Δ EDV) and end-systolic (Δ ESV) volumes are shown for control subjects *(closed circles)* and patients with aortic stenosis *(open circles)*.

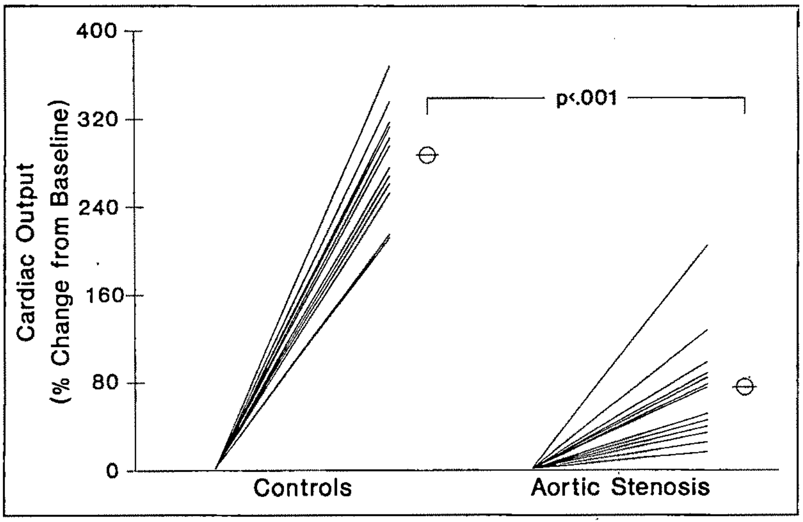

FIGURE 6. Changes in cardiac output from rest to peak supine exercise are shown for control subjects and patients with aortic stenosis.

exercise in 36 consecutive symptomatic adults with valvular AS, but found it to be of poor predictive accuracy with regard to severity of valve gradient. Nylander et al[23] exercised 76 adult patients with AS, all but 3 of whom were symptomatic, and found abnormal blood pressure hemodynamics in 62 (a decrease in blood pressure or limited increase of <10 mm Hg/30 W work load). No complications were encountered during exercise testing in this series of largely symptomatic adults with operable AS.

Compared with age- and sex-matched healthy control subjects, asymptomatic patients with valvular AS in the current study demonstrated impaired effort tolerance during graded treadmill exercise testing (by 20%) and reduced VO_2max and % predicted VO_2max (both by 28%). Maximal systolic blood pressure response of patients with AS was significantly lower than that of control subjects, with abnormal blood pressure responses developing in 9 patients. Ischemic-appearing ST-segment depression was frequently observed in our study (10 of 14 patients), was often dramatic (up to 5 mm) and was similarly prevalent in patients with (6 of 7) and without (4 of 6) LV hypertrophy on the electrocardiogram at rest (an additional patient without LV hypertrophy on electrocardiogram developed a right bundle branch block pattern during exercise). However, despite the ischemic appearance of the electrocardiographic response to exercise, thallium scans were entirely normal in 9 of 12 patients who underwent this study, although mild diffuse subendocardial ischemia cannot be excluded by thallium scintigraphy.

The asymptomatic patients in our study had marginally higher LV ejection fractions at rest than did control subjects. Borer et al[24] reported that LV ejection fractions in 26 symptomatic patients with AS determined by radionuclide angiography decreased from 67% at rest to 57% during exercise, and increased during exercise to 72% in 13 patients after aortic valve replacement. In our asymptomatic patients with AS, 4 demonstrated either no change or a decrease in ejection fraction as a consequence of abnormal end-systolic and end-diastolic volume changes during exercise. The relevance of this abnormal ejection fraction response to exercise is suggested by the lower oxygen consumption during exercise in these 4 patients compared with that in the 10 whose LV ejection fractions increased during exercise. The reduction in ejection fraction may in part be a consequence of myocardial ischemia, in that 2 of the 3 patients with a decrease in ejection fraction during exercise had reversible regional thallium defects during treadmill exercise. For most patients, effort limitation may have been a consequence of abnormal diastolic function. Subendocardial ischemia undetected by thallium scintigraphy may have contributed to abnormal diastolic function during stress. Peak filling rate at rest was significantly lower in patients than in control subjects. During exercise, end-diastolic volume actually decreased, and this compromise of diastolic filling volume during exercise along with a limited decrease in end-systolic volume resulted in an actual decrease in stroke volume during exercise. This decrease in stroke volume contributed to the marked limitation in cardiac

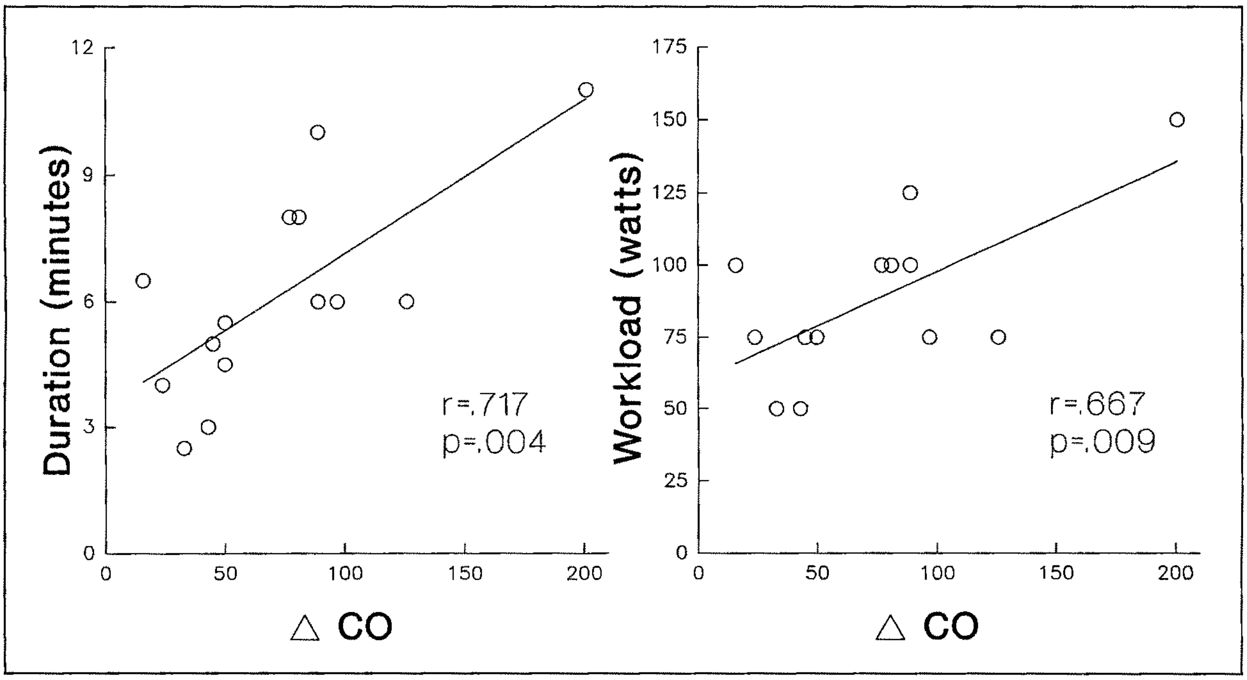

FIGURE 7. Changes in cardiac output (△ CO) in relation to supine exercise duration *(left)* and work load *(right)* are shown for study patients.

output response to exercise compared with that of control subjects which in turn correlated directly with the diminished effort duration and work load in the patients. Although relative and not absolute LV volume changes during exercise were measured in our study, the similar basal LV volumes for patients with AS and for control subjects support the relevance of our findings.

Limited stroke volume and cardiac output responses to supine bicycle exercise stress in symptomatic patients with severe valvular AS as a consequence of abnormal end-systolic and end-diastolic volume changes during exercise have been reported in previous studies.[25-29] The average 1% change in stroke volume (by Fick cardiac output determination) in 18 symptomatic patients studied by Anderson et al[25] is similar to the −6% change in stroke volume during exercise in our asymptomatic patients who also performed supine exercise. It has been noted in patients with AS after aortic valve replacement[30-31] and in patients with LV hypertrophy associated with hypertension[32] that the limitation in stroke volume response to exercise is largely a consequence of the inability to augment end-diastolic volume during stress.

Although a randomized study for operative valve replacement based on abnormal exercise hemodynamics versus awaiting the development of symptoms will probably never be performed, our findings of abnormal exercise responses in a subset of asymptomatic patients at least merit careful follow-up evaluations if a nonoperative "watchful waiting" approach is chosen. Conversely, excellent effort tolerance with normal exercise hemodynamics would seem reassuring to the physician and patient, and would permit less restriction of activities. Serial exercise testing may additionally allow identification of deterioration in cardiac compensation to AS, as well as detection of the subtle onset of symptoms.

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Doppler Echocardiographic Findings in Adults with Severe Symptomatic Valvular Aortic Stenosis

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Balloon Valvuloplasty Registry Echocardiographers*

Baseline echocardiographic data in 680 adults (mean age 78 years) undergoing balloon aortic valvuloplasty at 24 medical centers were analyzed to describe the degree of outflow obstruction in patients with symptomatic aortic stenosis. Maximal aortic jet velocity ranged from 2.3 to 6.6 m/s (mean 4.4 ± 0.8) and continuity equation valve area ranged from 0.1 to 1.4 cm^2 (mean 0.6 ± 0.2). Of note, 36% had a jet velocity $\leq$4.0 m/s but only 3% had a valve area >1.0 cm^2 due to a high prevalence of impaired systolic function (54%). Outflow tract diameter was poorly correlated with body surface area ($p = 0.26$), although the group mean diameter was smaller in women than in men (1.9 ± 0.2 vs 2.1 ± 0.3 cm, $p = 0.0001$).

Mean pressure gradient was related closely to maximal gradient ($r = 0.92$) and to maximal jet velocity (mean $\Delta P = 2.4\ V^2 + 0.75$ mm Hg). Simpler measures of aortic stenosis severity were correlated with Doppler and invasive valve area as follows: maximal jet velocity ($r = -0.36$ and -0.32), mean gradient ($r = -0.33$ and -0.29), outflow tract to jet velocity ratio ($r = 0.67$ and 0.40), and the fractional shortening velocity ratio ($r = 0.29$ and 0.22).

This study demonstrates marked variability in stenosis severity in symptomatic adults referred for balloon aortic valvuloplasty. The absence of a predictable relation between outflow tract diameter and body size emphasizes the importance of this measurement in each patient if definition of valve area is needed. The correlations between mean pressure gradient and maximal jet velocity, and between valve area and the velocity ratio support the potential use of these simpler measures of stenosis severity.

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Doppler echocardiographic techniques now are accepted clinical methods for evaluation of aortic stenosis severity in symptomatic adults.[1–3] Transaortic pressure gradients, calculated from flow velocities using the Bernoulli equation, and valve areas, determined by the continuity equation, have been well validated compared with manometric pressure gradients and Gorlin formula valve areas in animal models,[4,5] in patients with a wide range of stenosis severity,[6–11] and in adults undergoing balloon valvuloplasty.[12,13] Several previous studies have suggested that simpler descriptors of stenosis severity — including aortic jet maximal velocity,[14] the ratio of maximal velocities in the outflow tract and aortic jet,[8,10] use of maximal velocities instead of velocity-time integrals in the continuity equation,[9,15] mean pressure gradient calculated from an empirically determined regression equation[14] and the fractional shortening-velocity ratio[16] — may be as useful in clinical decision-making as continuity equation valve areas and measured mean pressure gradients. This study examines the baseline Doppler echocardiographic data in symptomatic adults undergoing balloon aortic valvuloplasty at 24 medical centers to: (1) describe the variability in severity of aortic stenosis and other echocardiographic findings in symptomatic patients; (2) evaluate the relation of outflow tract diameter to body size and to stenosis severity in adults with severe symptoms; and (3) examine the relation between complex and simplified Doppler measures of stenosis severity.

METHODS

Patient population: The Balloon Valvuloplasty Registry included adults undergoing aortic valvuloplasty at 24 medical centers between November 1, 1987, and

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*See Appendix for list of Balloon Valvuloplasty Registry Echocardiographers.

TABLE I Baseline Doppler and Echocardiographic Data in Patients Undergoing Balloon Aortic Valvuloplasty (n = 680)

Variable	Mean ± 1 SD	Range
Aortic stenosis maximal jet velocity (m/s)	4.4 ± 0.8	2.3–6.6
Mean pressure gradient (mm Hg)	48 ± 18	13–120
Maximal pressure gradient (mm Hg)	79 ± 30	21–174
Left ventricular outflow tract maximal velocity (m/s)	0.82 ± 0.22	0.3–1.6
Left ventricular outflow tract diameter (cm)	2.0 ± 0.3	1.1–3.2
Aortic valve area (cm²)	0.6 ± 0.2	0.1–1.4
Aortic valve index (cm²/m²)	0.35 ± 0.12	0.06–0.92
Left atrial size (cm)	45 ± 9	21–85
Left ventricular dimensions (mm)		
Diastole	51 ± 10	27–141
Systole	36 ± 12	14–79
Fractional shortening (%)	29 ± 12	2–72

October 30, 1989. All subjects gave informed consent and the study protocol was approved by each institution's review board. The current study is based on the 680 patients undergoing aortic valvuloplasty with baseline echocardiographic data (interval between echocardiography and valvuloplasty 3 ± 6 days). Age range was 24 to 103 years (mean 78) with 42% men and 58% women. Symptomatically, 23% of patients had mild or no heart failure symptoms, whereas 76% were in New York Heart Association class III to IV (1% unknown).

Doppler echocardiography: The echocardiographic data were recorded and analyzed at each medical center using strictly defined standards agreed to by each echocardiographer. Aortic stenosis jet maximal velocity was recorded with continuous-wave Doppler ultrasound from the window yielding the highest frequency shift with careful patient positioning and transducer angulation to obtain a parallel intercept angle between the ultrasound beam and aortic jet. Left ventricular outflow tract (LVOT) velocity was recorded with pulsed Doppler ultrasound from an apical approach with the sample volume (5 to 10 mm in length) positioned just proximal to the stenotic valve (documented by recording the aortic closing click). Outflow tract diameter (D) was measured in midsystole from a parasternal long-axis view, parallel and just proximal to the aortic valve. Cross-sectional area (CSA) was calculated as:

$$CSA_{LVOT} = \pi(D/2)^2 \tag{1}$$

All measurements were averaged from 3 to 5 beats for regular rhythms (78%) and from 5 to 10 beats for irregular rhythms (20%).

Aortic valve area (AVA) was calculated using velocity time integrals (VTI) in the continuity equation (15%):

$$AVA = (VTI_{LVOT}/VTI_{AS}) \times CSA_{LVOT} \tag{2}$$

or maximal velocities (V) in the simplified continuity equation (85%):

$$AVA = (V_{LVOT}/V_{AS}) \times CSA_{LVOT} \tag{3}$$

Mean transaortic pressure gradient (ΔP) was determined by averaging the instantaneous gradients over the systolic ejection period, calculated with the Bernoulli equation:

$$\Delta P = 4V^2 \tag{4}$$

Left ventricular internal dimensions and left atrial size were measured by M-mode echocardiography. Fractional shortening (% FS) was calculated as the difference between end-diastolic and end-systolic dimensions, divided by end-diastolic dimension. Left ventricular hypertrophy was defined as a mean wall thickness ≥12 mm. Overall systolic function was qualitatively assessed by an experienced observer as normal, or mildly, moderately or severely reduced. The presence of segmental wall motion abnormalities was noted. Aortic

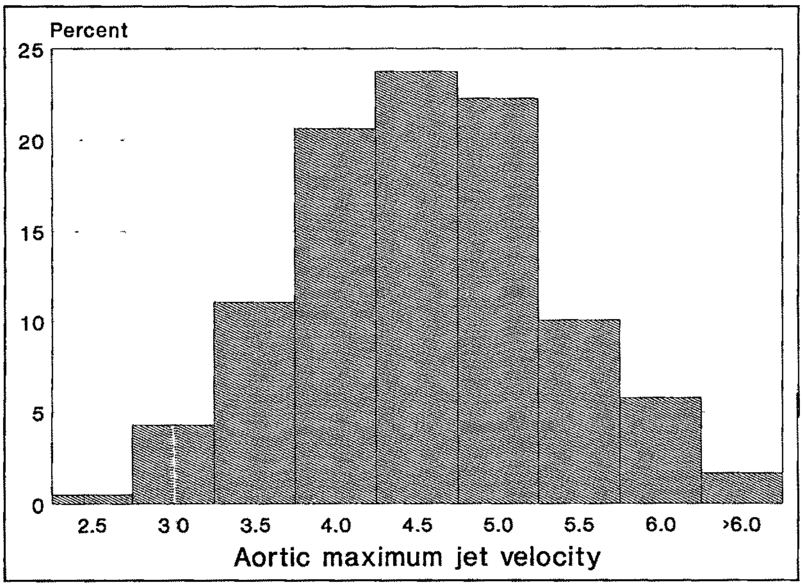

FIGURE 1. Bar graph of distribution of aortic maximal jet velocity.

and mitral regurgitation were evaluated with conventional pulsed or color Doppler flow imaging, with grading of severity (none, mild, moderate or severe) using standard criteria.[17]

Potential simpler measures of the severity of aortic stenosis evaluated in this study were maximal jet velocity,[14] maximal and mean pressure gradients, maximal outflow tract velocity to maximal aortic jet velocity ratio[8,10,14]:

$$\text{Velocity ratio} = V_{LVOT}/V_{AS} \qquad (5)$$

and the fractional shortening velocity ratio[16]:

$$\text{FSVR} = \%\text{FS}/4V^2 \qquad (6)$$

Invasive data: Valve area was calculated at catheterization immediately before valvuloplasty with either the Gorlin or Hakki formula using Fick, thermodilution, or green dye cardiac output and the transaortic pressure gradient data.

Data analysis: Data are expressed as means ± 1 standard deviation. Measurements were compared with each other by correlation coefficients. Means in subgroups were compared by *t* test. Correlations were transformed to the normal distribution and compared between subgroups by a test of equality of means of independent normally distributed random variables.[18]

RESULTS

Baseline data (Table I): The range of maximal aortic jet velocities was wide in these symptomatic adults — 221 of 606 (36%) had a jet velocity ≤4.0 m/s (Figure 1); only 21 of 606 (3%) had a jet velocity <3.0 m/s. The range of mean pressure gradients also was large. Although the range of valve areas is narrower, 16 of 524 (3%) had a valve area >1.0 cm^2, yet had significant symptoms attributed to valvular aortic stenosis. The range of aortic valve areas is 0.06 to 0.92 cm^2/m^2 when indexed to body surface area. The range of invasive data was similar with mean pressure gradients of 12 to 136 mm Hg (mean 55 ± 21) and valve areas of 0.1 to 1.4 cm^2 (mean 0.51 ± 0.20). Other echocardiographic findings are summarized in Table II.

TABLE II Prevalence of Associated Echocardiographic Findings in Patients with Aortic Stenosis

Variable	No. of Pts. with Finding/Total (%)
Aortic regurgitation	512/658 (78)
Mild	392/658 (60)
Moderate	117/658 (18)
Severe	3/658 (0.5)
Mitral regurgitation	495/647 (77)
Mild	283/647 (44)
Moderate	160/647 (25)
Severe	52/647 (8)
Left ventricular hypertrophy	397/530 (75)
Segmental wall motion abnormalities	214/670 (32)
Left ventricular systolic function	
Normal	246/542 (45)
Mildly reduced	103/542 (19)
Moderately reduced	86/542 (16)
Severely reduced	107/542 (20)

Outflow tract diameter: Outflow tract diameter correlated poorly with body surface area (r = 0.26, Figure 2) or height (r = 0.22) in this adult population, although the group mean diameter for women (1.9 ± 0.2 cm) was smaller than for men (2.1 ± 0.3 cm, p = 0.0001). Outflow tract diameter was not related to left ventricular internal dimensions (r = 0.19) in this population. Repeat measurement of outflow tract diameter

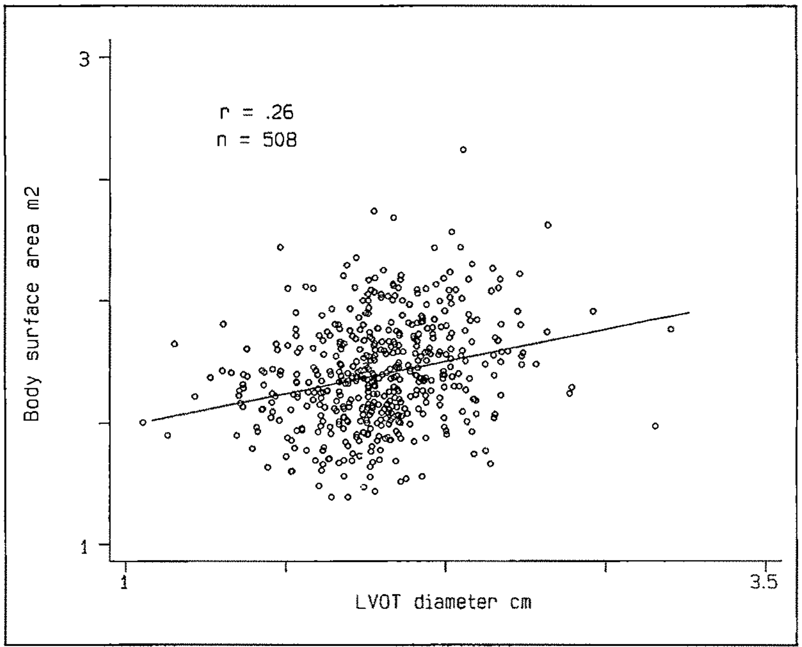

FIGURE 2. Left ventricular outflow tract (LVOT) diameter (x axis in centimeters) versus body surface area (y axis in meters squared).

after valvuloplasty showed little difference from the baseline measurement (r = 0.92, y = 0.94x + 0.11 cm, Figure 3).

Pressure gradients/jet velocity: Mean pressure gradient is related to Doppler and invasive valve areas (r = −0.33 and −0.29). Note that mean transaortic pressure gradient is related closely to maximal pressure gradient (n = 589, r = 0.92; mean pressure gradient = 0.60 maximal pressure gradient + 0.75 mm Hg) and to maximal aortic jet velocity (r = 0.92, mean pressure gradient = $2.4V^2$ + 0.75 mm Hg) (Figure 4). Aortic jet maximal velocity correlated with Doppler and invasive aortic valve area (r = −0.36 and −0.32). Of the 326 patients with a jet velocity >4.0 m/s, 98% had a Doppler valve area ≤1.0 cm^2. Of the 162 patients with a jet velocity of 3.0 to 4.0 m/s, 96% had a valve area <1.0 cm^2.

Simpler measures of aortic stenosis severity: To evaluate the importance of the components of the continuity equation in valve area calculation, outflow tract cross-sectional area (CSA_{LVOT}) and the outflow tract velocity to aortic jet velocity ratio (V_{LVOT}/V_{AS}) were compared with both Doppler and invasive valve areas. Not surprisingly, outflow tract cross-sectional area is related to Doppler valve area (r = 0.51, Figure 5) but it is less closely related to invasive valve area (r = 0.19). However, the velocity ratio is related to both Doppler (r = 0.67, Figures 6 and 7) and invasive valve areas (r = 0.40).

The relation between Doppler and invasive valve areas and the fractional shortening velocity ratio was less strong (r = 0.29 and 0.22). A fractional shortening velocity ratio <0.8 identified 239 of 307 patients with a valve area <0.7 cm^2 (sensitivity = 78%) and a ratio ≥0.8 identified 38 of the 75 patients with a valve area ≥0.7 cm^2 (specificity = 51%).

Influence of coexisting aortic regurgitation: The correlation between valve area and outflow tract to aortic jet velocity ratio was not significantly (p = 0.12) larger for 381 patients with no or mild aortic regurgitation (r = 0.56) compared with 98 patients with moderate to severe aortic regurgitation (r = 0.67). The correlation between maximal and mean pressure gradients was no different (p = 0.12) for 468 patients with no or mild regurgitation (r = 0.92) than for 108 patients with moderate to severe aortic regurgitation (r = 0.89).

DISCUSSION

This study demonstrates marked variability in the severity of outflow obstruction in symptomatic adults with valvular aortic stenosis referred for balloon valvuloplasty. Because intervention typically is considered soon after the onset of symptoms, this suggests that symptom onset occurs with different degrees of stenosis severity in different individuals. This finding is in concordance with previous studies that have shown a marked overlap in measures of stenosis severity between symptomatic and asymptomatic adults with valvular aortic stenosis.[19-22] This variability is not explained entirely by body size, because indexing valve area to body surface area only slightly narrows the scatter of the data.

The correlation between Doppler maximal and mean transaortic pressure gradients, based on the similar shape of the velocity time curve in adults with severe aortic stenosis, deserves emphasis. This relation cannot

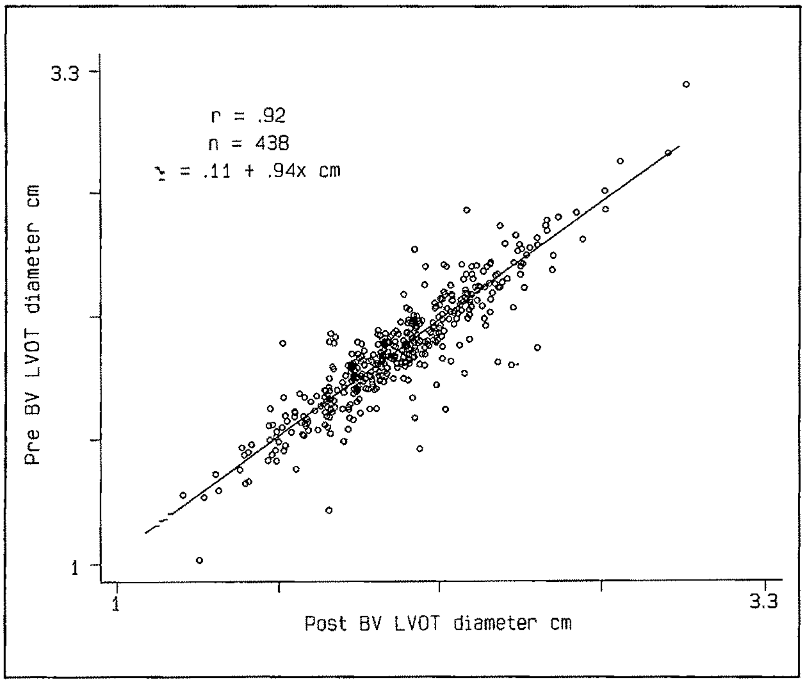

FIGURE 3. Reproducibility of left ventricular outflow tract (LVOT) diameter measurements comparing the pre- (x axis) and postvalvuloplasties (y axis) with 2-dimensional echocardiographic measurements. BV = balloon valvuloplasty.

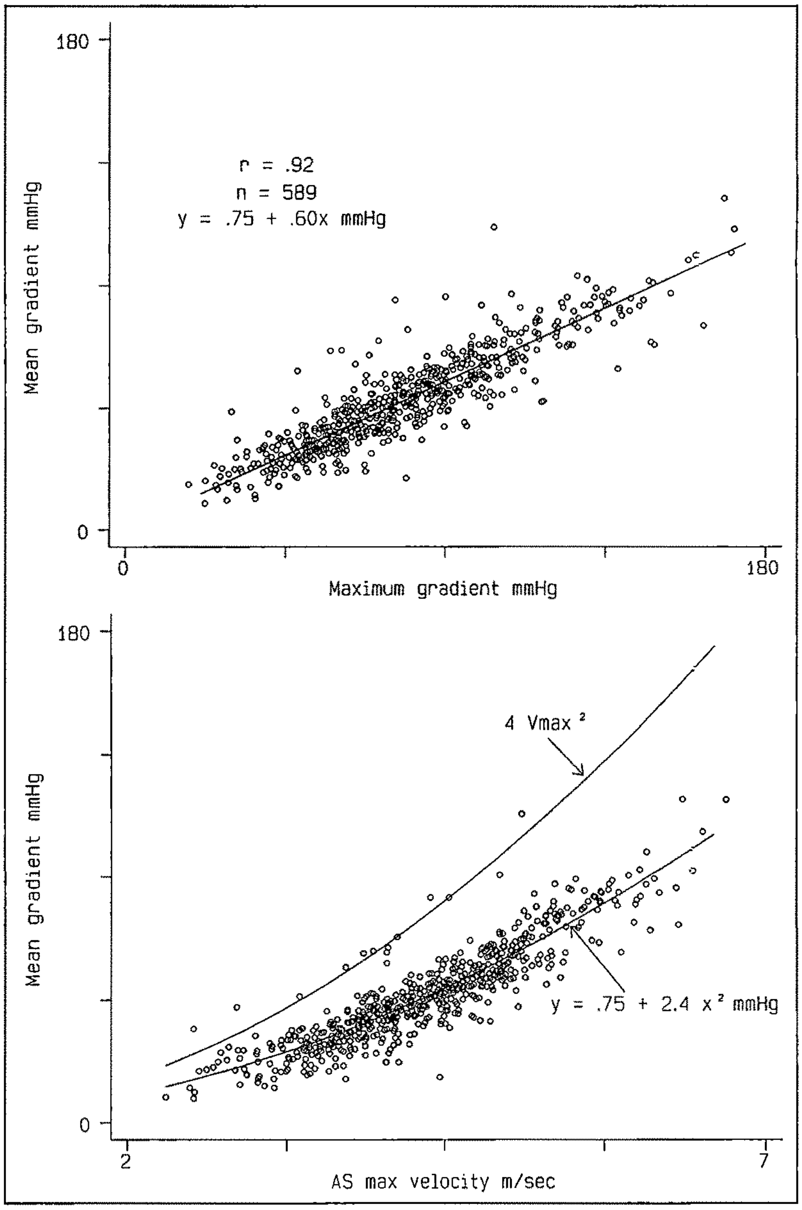

FIGURE 4. ***Top,*** **Doppler maximal instantaneous gradient (x axis) versus Doppler mean transaortic pressure gradient (y axis).** ***Bottom,*** **aortic stenosis (AS) maximal (max) jet velocity (x axis) versus Doppler mean transaortic pressure gradient (y axis).**

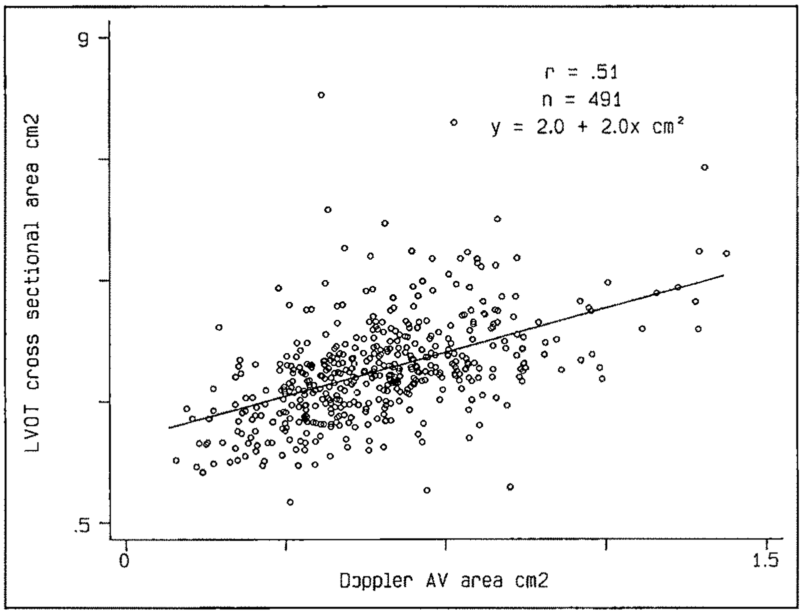

FIGURE 5. Aortic valve (AV) area (x axis) versus left ventricular outflow tract (LVOT) cross-sectional area (y axis).

necessarily be extended to other clinical settings in which the shape of the velocity curve may be different (e.g., normal or dysfunctional prosthetic valves).

The importance of considering transaortic volume flow rate in describing aortic stenosis severity is underlined in this study. Fully 36% of these patients with severe symptomatic valvular obstruction had a mean transaortic pressure gradient <40 mm Hg and 36% had a maximal aortic jet velocity ≤4.0 m/s. Calculation of valve areas with the continuity equation, which incorporates transaortic volume flow, shows that valve area is significantly decreased and that low pressure gradients (and velocities) are due to low transaortic volume flow in this patient subgroup.

Recording and measuring the data for calculating continuity equation valve areas can be time consuming and tedious, so that simpler methods for accurately assessing stenosis severity would be useful clinically. The outflow tract diameter is the most difficult variable to measure and shows the greatest intra- and interobserver measurement variability.[9,19] Unfortunately, the current study demonstrates a poor correlation between body size and outflow tract diameter. Thus, accurate continuity equation valve area calculations continue to require an accurate measurement of outflow tract diameter in each patient.

Whereas evaluation of simpler measures of stenosis severity is somewhat problematic given that all these patients had severe stenosis, some insights can be derived from these data. The relative increase in anterograde velocity as blood is ejected from the outflow tract across the narrowed aortic valve (i.e., deleting outflow tract cross-sectional area from the continuity equation) is inversely correlated with valve area. This observation

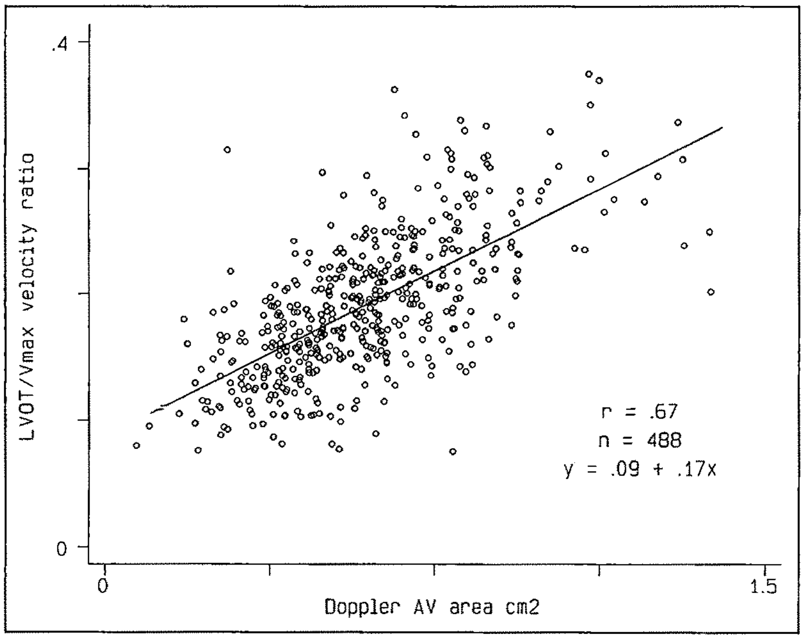

FIGURE 6. Aortic valve (AV) area (x axis) versus velocity ratio (y axis). LVOT = left ventricular outflow tract; Vmax = maximal velocity.

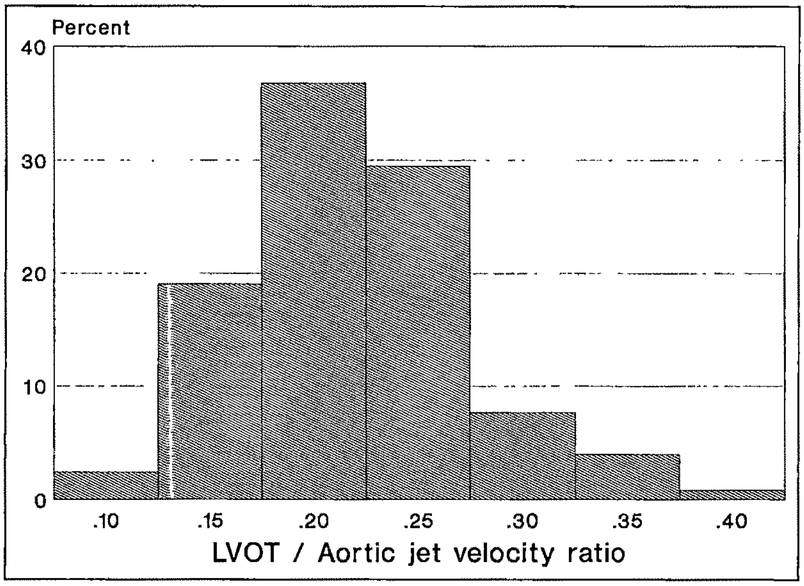

FIGURE 7. Bar graph of distribution of left ventricular outflow tract (LVOT)/aortic jet velocity ratio.

raises the possibility that, in effect, this velocity ratio already is "indexed" for body size, and is congruent with the suggestion that the subaortic diameter can be used to normalize left ventricular and left atrial dimensions.[23]

The variability in the degree of outflow obstruction observed in these symptomatic patients focuses attention on the need to consider more than just valve gradient or area in fully defining the effects of the stenosis on ventricular function and the patient's symptomatic state. Left ventricular hypertrophy was absent, despite severe aortic stenosis, in 22% of our patients. The prevalence of reduced systolic function was high, but may be related to patterns of referral for aortic valvuloplasty. It has been suggested that left ventricular diastolic function, which was not evaluated in this study, correlates more closely with symptoms than do measures of outflow obstruction.[24] In this regard, then, there may be no advantage to a precise definition of valve area (by either invasive or noninvasive methods) compared with a simpler measure of the degree of outflow obstruction. Instead, evaluation of disease severity in an individual patient should include left ventricular systolic and diastolic function, and the severity of coexisting aortic and mitral regurgitation (which were prevalent in our population), as well as the degree of outflow obstruction.

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APPENDIX

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*Principal Investigator.

Doppler Echocardiographic Estimation of Mitral Valve Area During Changing Hemodynamic Conditions

Alan C. Braverman, MD, James D. Thomas, MD, and Richard T. Lee, MD

Patients with mitral stenosis often present during periods of hemodynamic stress such as pregnancy or infections. The Doppler pressure half-time method of mitral valve area (MVA) determination is dependent on the net atrioventricular compliance as well as the peak transmitral gradient. The continuity equation method of MVA determination is based on conservation of mass and may be less sensitive to changes in the hemodynamic state. To test this hypothesis, 17 patients admitted for catheterization with symptomatic mitral stenosis and no more than mild regurgitation underwent Doppler echocardiography at rest and during supine bicycle exercise targeted to an increase in heart rate by 20 to 30 beats/minute. Net atrioventricular compliance was also estimated noninvasively. Cardiac output and transmitral gradient increased significantly during exercise ($p < 0.001$), while net atrioventricular compliance decreased ($p < 0.001$). MVA by the pressure half-time method increased significantly during exercise from 1.0 ± 0.2 to 1.4 ± 0.4 cm^2 ($p < 0.001$). There was no significant difference in MVA estimation using the continuity equation comparing rest to exercise, with the mean area remaining constant at 0.8 ± 0.3 cm^2 ($p = 0.83$). Thus, during conditions of changing hemodynamics, the continuity equation method for estimating MVA may be preferable to the pressure half-time method.

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The Doppler echocardiographic pressure half-time method of mitral valve area (MVA) determination has gained widespread acceptance and is based on a relation first described by Libanoff and Rodbard[1] and further developed by Hatle et al.[2,3] Although this method has proved to be useful in estimating MVA in native[4] and prosthetic valves[5] the pressure half-time method may be inaccurate in certain clinical settings such as with exercise,[1,3] pregnancy,[6] aortic insufficiency,[7,8] poor left ventricular compliance,[9] or acutely after mitral valvuloplasty.[10,11] Flachskampf et al[8] and Thomas et al[10,12] found the pressure half-time to be dependent not only on MVA, but also on the net atrioventricular compliance as well as the peak transmitral gradient.

The continuity equation method has been demonstrated to be a reliable and accurate method of calculating MVA.[13,14] The continuity equation is based on conservation of mass[7] and is theoretically independent of transvalvar gradient and atrioventricular compliance.[15] Many patients with mitral stenosis first present clinically during periods of hemodynamic stress such as with infections, pregnancy or tachycardia; noninvasive determination of MVA using the continuity equation method may be more reliable than the pressure half-time method during changing hemodynamic states. To test this hypothesis, a minor exercise protocol was used as a model of changing hemodynamics to compare the pressure half-time and continuity equation methods in patients with symptomatic mitral stenosis and no more than mild mitral regurgitation.

METHODS

Study patients: From November 1989 to February 1991, 40 patients with symptomatic native mitral valve stenosis underwent diagnostic cardiac catheterization at Brigham and Women's Hospital. This study was performed in a subset of 17 patients with mitral stenosis as the predominant lesion. The 23 patients who did not participate in the study were excluded for the following reasons: (1) severe aortic stenosis (n = 8, mean area 0.6 cm^2); (2) >2+ mitral regurgitation by Doppler echocardiogram[16,17] or left ventriculogram[18] on a 0 to 4+ scale (n = 3); (3) poor quality echocardiographic images (n = 2); (4) inability to exercise (n = 4); and (5)

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logistic reasons/declined participation (n = 6). The 17 study patients ranged in age from 30 to 83 years old (mean 59 ± 14). Ten patients had sinus rhythm and 7 had atrial fibrillation. One patient had undergone prior surgical commissurotomy 7 years earlier, and no patient had prior balloon valvuloplasty. All patients underwent diagnostic cardiac catheterization with coronary angiography within 24 hours of echocardiography. No patient had >2+ aortic insufficiency by Doppler echocardiogram on a 0 to 4+ scale.[19,20] All patients in this study had normal left ventricular function and no patient had symptomatic ischemic heart disease. The study was approved by the Brigham and Women's Hospital Committee for the Protection of Human Subjects from Research Risks, and written informed consent was obtained from each patient.

Echocardiographic examination: Two-dimensional echocardiograms at rest were recorded using a Hewlett Packard 77020 AC/AR phased-array ultrasonoscope device with a 2.5 MHz transducer. Standard parasternal short- and long-axis and apical 4- and 5-chamber views were recorded. The presence of aortic insufficiency and mitral regurgitation was carefully sought and semiquantitated by pulsed-wave and color Doppler mapping as previously described.[19,20] Left ventricular outflow velocity was recorded using pulsed-wave Doppler from the apical view. In the 2 patients with >1+ aortic insufficiency, pulmonary artery flow was recorded at the level of the anulus. Diastolic flow velocity across the stenotic mitral valve was recorded using imaging continuous-wave Doppler and color Doppler flow mapping to align the continuous wave beam with the mitral stenosis jet. No angle correction was attempted for the plane orthogonal to the 2-dimensional imaging plane.

Using a Cardiology Workstation (GTI Freeland Medical Division, Indianapolis, Indiana), 5 to 10 high-quality cardiac cycles were digitized and averaged. All Doppler profiles were digitized by a single investigator unaware of the catheterization results. The peak and mean transmitral gradients were calculated using the modified Bernoulli equation.[3] Diameter of the left ventricular outflow tract was measured from the parasternal long-axis view in systole, from trailing edge to leading edge.[7] In the 2 patients with >1+ aortic insufficiency, pulmonary artery diameter was measured as previously described.[21] The cross-sectional area of the aortic or pulmonic anulus was calculated as: area = (π) $(\text{diameter}/2)^2$.

Stroke volume was calculated as the product of the cross-sectional area of the left ventricular or pulmonary outflow tract and the velocity time integral of that outflow tract.[22] Cardiac output was calculated as the product of the stroke volume and heart rate. Using the continuity equation method, the MVA was calculated by dividing the stroke volume through the left ventricular or pulmonary outflow tract by the velocity time integral of the diastolic flow through the mitral valve, as previously described.[7,13] MVA was also determined by the pressure half-time method of Hatle et al.[2,3] The mitral pressure half-time was obtained by calculating the time required for the peak transmitral velocity to decrease to a value equal to the square root of one-half of the peak value. MVA was calculated using the formula: MVA = 220/pressure half-time (in milliseconds), where 220 is an empiric constant.[3]

The net atrioventricular compliance was determined noninvasively for each patient at rest and during exercise by applying a formula derived by Thomas et al.[10] Using 2-dimensional and Doppler echocardiographic measurements, the net atrioventricular compliance can be estimated as follows:

$$\text{Net compliance} = \frac{(\text{pressure half-time})(\text{effective MVA})}{(11.6)(\text{peak transmitral gradient})^{1/2}}$$

where the pressure half-time is expressed in milliseconds, the peak transmitral gradient in mm Hg, the effective MVA (in cm^2) is calculated using the continuity equation, and the net atrioventricular compliance is expressed in ml/mm Hg.

Exercise protocol: Immediately after the echocardiogram at rest, an exercise echocardiographic protocol was performed. Each patient performed supine bicycle exercise at a constant work load for a time period ≤5 minutes, targeted to a peak heart rate of 20 to 30 beats/min above the baseline heart rate. The resistance on the bicycle was negligible, and no patient achieved a work load of 25 W, the lowest reading on the bicycle. When the target heart rate was achieved, the Doppler echocardiographic measurements (left ventricular or pulmonary outflow tract velocity by pulsed-wave Doppler and transmitral flow velocity by imaging continuous-wave Doppler) were again recorded. All exercise Doppler data were recorded on ½-inch videotape in a time period <1 minute. Five to 10 high-quality cycles were digitized and averaged to calculate peak and mean transmitral gradient, cardiac output and MVA using the continuity equation and pressure half-time methods. In addition, the net atrioventricular compliance during exercise was calculated. The outflow tract diameters were not remeasured during exercise, but were assumed to remain constant during this minor exercise. To complete all measurements within 1 minute, planimetry of the mitral valve was not included in the protocol.

Cardiac catheterization: All patients underwent right- and left-sided cardiac catheterization to determine MVA at rest using the modified Gorlin formula[23]; no exercise was performed in the catheterization

TABLE I Doppler Parameters

	Rest				Exercise			
Pt. No.	Peak Grad.	PHT MVA	Net Comp.	CE MVA	Peak Grad.	PHT MVA	Net Comp.	CE MVA
1	7	1.3	8.4	1.5	7	1.6	6.9	1.5
2	20	0.9	4.6	1.0	27	1.2	3.3	1.0
3	23	0.9	3.8	0.9	31	1.1	2.7	0.8
4	17	1.0	3.1	0.7	20	1.1	2.5	0.7
5	21	1.4	2.6	0.8	35	1.8	1.6	0.9
6	31	1.1	2.1	0.7	34	1.2	1.8	0.6
7	18	1.0	2.4	0.5	20	1.4	1.8	0.6
8	9	0.9	7.9	1.1	21	1.3	3.7	1.2
9	26	0.8	3.4	0.7	42	1.1	1.8	0.7
10	23	0.8	1.7	0.4	30	1.2	1.1	0.4
11	16	1.1	3.2	0.7	25	1.2	2.4	0.7
12	11	1.3	5.7	1.3	18	1.6	3.7	1.1
13	7	0.9	8.1	1.1	15	2.5	4.9	0.9
14	27	0.9	2.1	0.5	39	1.2	1.5	0.6
15	14	0.8	5.0	0.8	18	1.2	3.2	0.8
16	18	0.9	2.4	0.5	27	1.1	1.5	0.5
17	19	1.2	3.5	1.0	28	1.2	3.4	1.1
Mean	18.1	1.0	4.1	0.8	25.7*	1.4*	2.8*	0.8
± SD	6.7	0.2	2.1	0.3	8.8	0.3	1.4	0.3

*$p < 0.001$ versus rest.
CE MVA = continuity equation mitral valve area in cm^2; Net Comp. = net atrioventricular compliance in ml/mm Hg; Peak Grad. = peak transmitral gradient; PHT MVA = pressure half-time mitral valve area in cm^2.

laboratory. Cardiac output was determined with the Fick method using measured oxygen consumption.[24] The transmitral pressure gradient was calculated by planimetric determination of left ventricular and pulmonary artery wedge pressures, simultaneously recorded at a paper speed of 100 mm/s using a standard fluid-filled manometer system. Five cycles were averaged in patients with sinus rhythm and 10 cycles were averaged in patients with atrial fibrillation. Left ventriculography was performed in 14 of the 17 patients. The severity of mitral regurgitation was graded on a 0 to 4+ scale, as previously described.[18]

Statistics: Values are expressed as mean ± 1 standard deviation. The significance of differences between paired measurements was assessed with paired Student's *t* tests. Linear regression analysis was used for comparisons of catheterization and echocardiographic methods. Because linear regression can be misleading when comparing 2 methods of clinical measurement, the method of Bland and Altman[25] was also used to compare estimates of MVA. A p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics: Mean MVA was 0.9 ± 0.4 cm^2 (range 0.2 to 2.0) using the Gorlin formula at catheterization. Mean echocardiographic MVA at rest was 1.0 ± 0.2 cm^2 (range 0.8 to 1.4) using the pressure half-time method, and 0.8 ± 0.3 cm^2 (range 0.4 to 1.5) using the continuity equation method. By Doppler echocardiography, 10 patients had no mitral regurgitation, 5 patients had 1+ mitral regurgitation, and 2 patients had 2+ mitral regurgitation. By Doppler echocardiography, 10 patients had no aortic insufficiency, 5 patients had 1+ aortic insufficiency, and 2 patients had 2+ aortic insufficiency. Mild aortic stenosis was present in 2 patients with peak instantaneous Doppler echocardiographic gradients of 25 mm Hg. Left ventriculography was performed in 14 patients: 9 had no mitral regurgitation, 3 had 1+ mitral regurgitation, and 2 patients had 2+ mitral regurgitation.

Exercise echocardiography: Doppler echocardiography demonstrated significant changes in hemodynamic conditions during exercise. Heart rate increased from 70 ± 14 at rest to 96 ± 18 beats/min during exercise ($p < 0.001$). Cardiac output increased from 4.3 ± 1.4 liters/min at rest to 5.1 ± 1.7 liters/min during exercise ($p < 0.001$). Mean transmitral gradient increased from 9 ± 4 mm Hg at rest to 14 ± 5 mm Hg during exercise ($p < 0.001$). MVA using the pressure half-time method increased from 1.0 ± 0.2 to 1.4 ± 0.3 cm^2 (Table I). MVA estimation by the pressure half-time method increased significantly during exercise, with a mean increase of 0.4 ± 0.5 cm^2 ($p < 0.001$) (Figure 1). The amount of increase in MVA ranged from a minimum of no change in 1 patient to a maximum of 1.6 cm^2 in another. There was no significant difference in MVA estimation using the continuity equation when comparing rest with exercise ($p = 0.83$), with the mean valve area remaining constant at 0.8 ± 0.3 cm^2 (Figure 2). In 16 of the 17 patients, MVA calculation by the continuity equation during exercise was within 0.1 cm^2 of the MVA at rest. Net atrioventricular compliance was estimated noninvasively in each patient at rest and during exercise and decreased significantly from 4.1 ± 2.1 to 2.8 ± 1.4 ml/mm Hg when comparing rest with exercise ($p < 0.001$) (Figure 3).

Noninvasive versus Gorlin-derived mitral valve area: For all 17 patients, there was a moderate correlation between the Gorlin-derived MVA and the resting Doppler pressure half-time area ($r = 0.58$, $y = 0.25x + 0.78$); the mean difference between the 2 methods (half-time area minus Gorlin area) was 0.1 ± 0.3 cm^2. The correlation between the Gorlin-derived area and the resting continuity equation area was better ($r = 0.73$, mean difference −0.1 ± 0.3 cm^2). During exercise, the pressure half-time MVA overestimated the resting Gorlin-derived MVA. Furthermore, the correlation between the pressure half-time MVA during exercise and the resting Gorlin-derived valve area was poor ($r = 0.12$, mean difference 0.4 ± 0.5 cm^2). However, the continuity equation MVA during exercise continued to correlate with the resting Gorlin-derived area despite the changes in hemodynamic state ($r = 0.70$, mean difference −0.1 ± 0.3 cm^2).

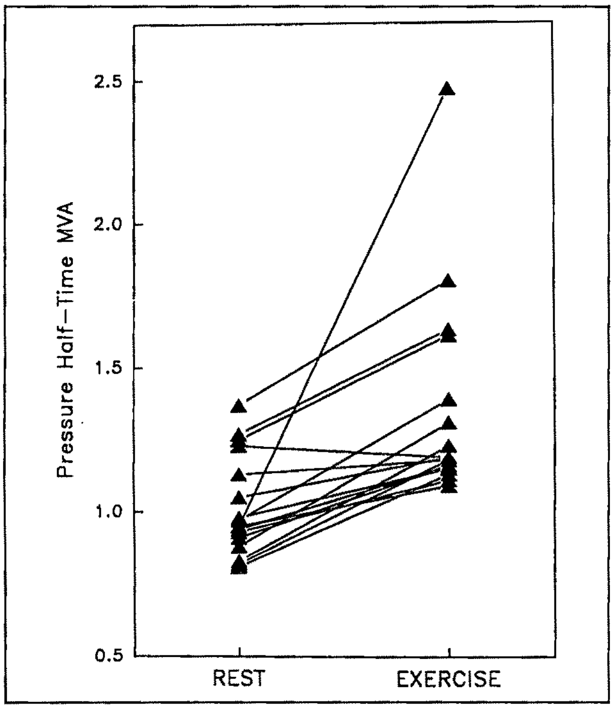

FIGURE 1. Mitral valve area (MVA) determinations (in cm^2) using the Doppler pressure half-time method at rest and during exercise for each of the 17 patients in this study.

DISCUSSION

This study compared 2 Doppler echocardiographic methods for determining MVA in patients with mitral stenosis at rest and during exercise and demonstrated that the continuity equation method, unlike the pressure half-time method, was not changed by exercise. Exercise-induced decreases in transmitral pressure half-times have been noted in earlier studies.[1,3] These data are also consistent with previous reports demonstrating the dependence of the pressure half-time on hemodynamic variables, such as transmitral gradient and atrioventricular compliance.[8-12]

In patients with severe rheumatic mitral stenosis, the mitral valve leaflets are thickened and stiff; our current understanding of mitral stenosis suggests that MVA is relatively fixed in an individual patient. Because the Doppler pressure half-time decreases and the peak transmitral gradient increases during exercise,

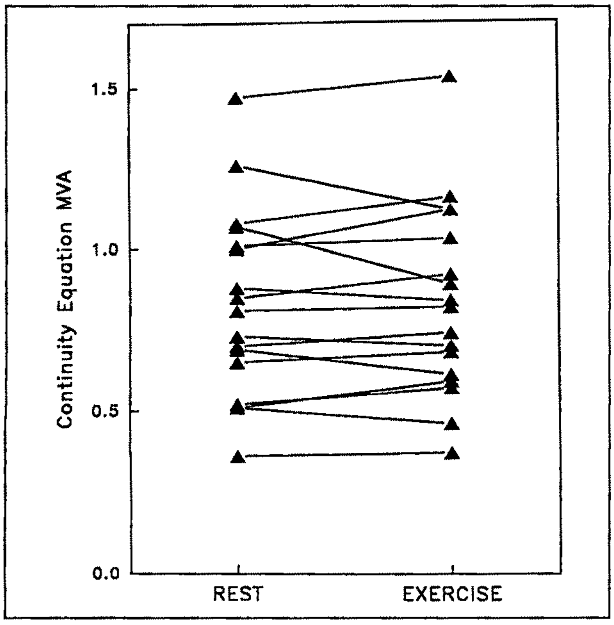

FIGURE 2. Mitral valve area (MVA) determinations (in cm^2) using the continuity equation method at rest and during exercise for each of the 17 patients in this study.

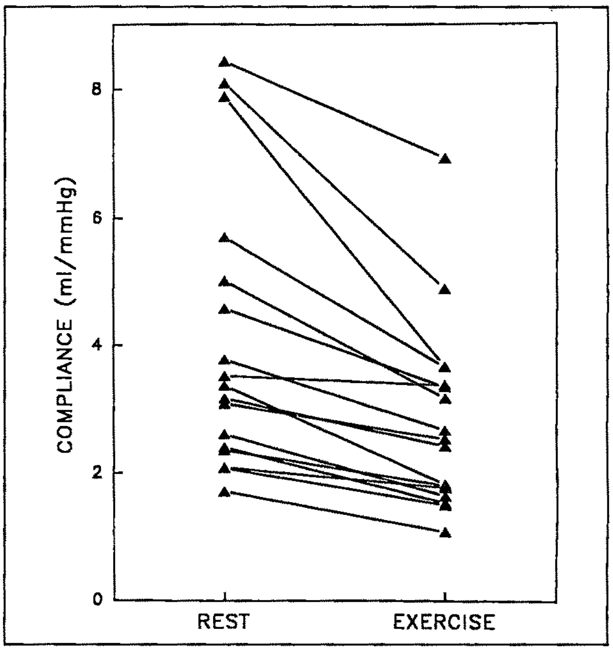

FIGURE 3. Net atrioventricular compliance at rest and during exercise for each of the patients in this study.

it follows that the net atrioventricular compliance decreases during exercise. The net atrioventricular compliance decreased significantly during exercise ($p < 0.001$) and offset the increase in peak transmitral gradient, resulting in a decrease in the measured Doppler pressure half-time. Although this study did not measure the atrial or ventricular compliance directly at rest or during exercise, it is likely that a marked decrease in left atrial compliance was responsible for the fall in net atrioventricular compliance during exercise. Chamber compliance in the heart is determined by the level of operating pressure and the curvilinear pressure-volume relation.[26] As the initial pressure increases, the slope of the tangent (operative chamber stiffness) increases.[26] In the patient with mitral stenosis, exercise leads to an increase in the initial transmitral pressure gradient, resulting in a shift to a steeper portion of the pressure-volume curve and diminished atrial operative compliance.

Study limitations: One reason that the pressure half-time method remains a useful tool for semiquantitating MVA noninvasively is that the continuity equation method is more difficult to perform. Potential errors in measuring outflow tract diameters or velocities may lead to errors in valve area determination. Because we considered it unlikely that minor exercise results in significant changes in outflow tract diameters, these measurements were assumed to remain constant. In addition, as defined by the conservation of mass, accurate MVA determination by 2-dimensional and Doppler echocardiography using the continuity equation requires that the flow volume across the stenotic valve and another valve (the valve used to calculate the stroke volume) be equal.[7,13] In patients with more than mild coexisting mitral regurgitation, the stroke volume measurement will be inaccurate, leading to an underestimation of MVA by the continuity equation method.[13] Because mild mitral regurgitation does not appear to have a significant effect on MVA using the continuity equation,[7] this should not have affected the results in our study. Coexisting aortic insufficiency results in an increase in stroke volume through the left ventricular outflow tract leading to an overestimation of the true MVA.[13] In the presence of moderate aortic insufficiency, the pulmonary outflow tract velocity should be used for stroke volume calculation.[7]

The correlations between noninvasive Doppler valve areas and Gorlin-derived catheterization MVA were only moderately good. Doppler echocardiograms were performed within 24 hours of the catheterizations; although the nonsimultaneous measurements may have partially explained the differences, potential errors in the invasive MVA calculations cannot be excluded. Errors of up to 20 to 40% may be obtained using the Gorlin formula for MVA determination.[9] In addition, valve areas of this relatively homogenous group of patients with moderate to severe mitral stenosis may have biased the analysis toward low correlation even when the measurements themselves were in good agreement. Finally, a minor degree of mitral regurgitation or aortic regurgitation present at rest could have potentially changed during exercise, resulting in a decrease in the Doppler pressure half-time. However, it is unlikely that these regurgitant lesions changed significantly, since the continuity equation method is also sensitive to mitral and aortic regurgitation and showed no significant changes during exercise.

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Late Results (30 to 35 Years) After Operative Closure of Isolated Ventricular Septal Defect from 1954 to 1960

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This study was designed to determine the clinical status, cause of death, and effects of pulmonary vascular disease and conduction abnormalities 30 to 35 years after surgery in 296 consecutive surviving patients of closure of ventricular septal defect. Of the 296 patients, current status was determined by contact with patient and physician in 290 cases, with 6 (2%) lost to follow-up (7,912 patient years are included). Cardiac catheterization after surgery in 168 patients showed complete closure of the defect in 80%. Death occurred in 59 patients (20%), with higher mortality rates in those operated on after the age of 5 years, those with pulmonary vascular resistance >7 units (51%), and those with complete heart block (78%). Of 37 patients with transient heart block after surgery, 8 (22%) have died (3 pulmonary vascular disease, 2 sudden death, 2 unknown causes and 1 complete heart block). Twenty other patients had a dysrrhythmia after surgery, and none of these died. Nine episodes of endocarditis occurred (11.4/10,000 patient years). Nine of 296 (3%) offspring had cardiac malformation. Most patients are in New York Heart Association class I, 57% attended college and 15% received an advanced degree.

The data show good results for this group of patients operated on during an early era (1954 to 1960) of open cardiac surgery. They support the current trend toward operation in patients with ventricular septal defects at an early age and with low pulmonary vascular resistance.

(Am J Cardiol 1991;68:1491–1497)

In 1954, the first successful closure of a ventricular septal defect (VSD) was performed by a group of surgeons at the University of Minnesota.[1] During the next 6 years, 341 patients underwent closure of VSD at our institution. Many of these patients survived the operation and are alive 30 to 35 years later. Groups of these patients have been the subject of previous reports,[2–7] but this study represents an attempt to determine the status of each of the surviving patients operated on during the period from 1954 to 1960. Whereas there have been a number of reports on patients after repair of VSD, often concerned with specific postoperative aspects such as pulmonary vascular resistance[7–16] and conduction disturbances,[17–23] none of these studies has extended for 30 to 35 years or has covered as large a sample of patients from this early era of cardiac surgery.

METHODS

Hospital records of 341 patients who underwent repair of VSD during the years 1954 through 1960 were reviewed and tabulated. Clinical status of patients after hospital discharge was determined through individual patient evaluation, or correspondence with the patient's relatives, personal physicians or other hospitals. Cardiac catheterization was recommended for each patient after surgery.[6] Current information was sought from all patients during the period from 1986 to 1989. If a patient had died, information was obtained from the family and personal physician regarding the circumstances of death, health status prior to death, and details of the postmortem examination, if performed.

The data were used to determine factors affecting survival and to calculate survival curves. Six of the 296 patients who were lost to follow-up were not included in the survival analysis. Survival curves were calculated by the Kaplen-Meier method, and groups were compared by means of the Breslow and Mantel tests. The first is more sensitive to early differences among the groups, and the second to later differences. Calculations of the expected number of deaths were based on tables from Health United States 1989, U.S. Department of Health and Human Services. The increase in survival rates over the years was taken into account. Because most of the patients were white, average rates for white

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TABLE I Ventricular Septal Defect After Surgery; Proportion of Long-Term Surviving Patients According to Age at Operation

Age at Operation (yrs)	No. of Patients	No. of Long-Term Surviving Patients
<2	26	23 (88%)
2–5	94	76 (81%)
6–10	111	84 (76%)
>10	59	48 (81%)
Total	290	231

males and females were chosen. A Biomedical-Designed Program and the Statistical Package for the Social Sciences were used for analysis.

Cox regression allows for adjustment for covariants. Candidates for predictor variables were: age at operation, pulmonary vascular resistance before surgery, and conduction disturbances after surgery. All 3 variables were statistically significant in a univariant as well as a multivariant model. Age was grouped into 5 categories (<2, 2 to 4, 4 to 6, 6 to 10, and >10 years) and then was treated as a continuous variable. Pulmonary vascular resistance was partitioned into groups <3, 3 to 5, 5 to 7, and >7 mm Hg/liter/min/m^2, with group scores of 0, 1, 2 and 4. Categories of conduction disturbances were described by contrasts that were assigned the following scores: normal = 0; right bundle branch block = 1; and remaining categories = 2.

RESULTS

Between March 26, 1954, and December 31, 1960, 341 patients with VSD underwent repair at the University of Minnesota Hospital. Of the 341 patients, 45 (13%) died after surgery, and the remaining 296 were discharged from the hospital. The current status of 290 of the 296 patients is known, with only 6 being lost to follow-up. In all, 7,912 postoperative years of follow-up are reported.

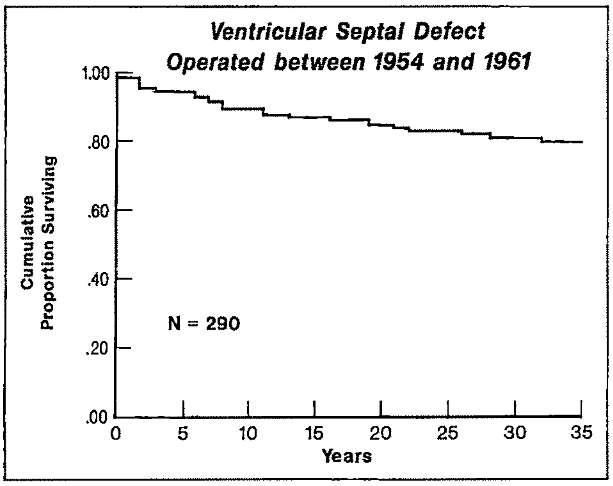

FIGURE 1. Ventricular septal defect after surgery. Life table analysis of 290 survivors.

TABLE II Ventricular Septal Defect After Surgery; Cause and Decade of Death in 59 Patients

	Interval from Operation (yrs)				
Cause	0–9	10–19	20–29	30	Total
Heart block	7	2	1	—	10
Reoperation	8	—	1	—	9
PVOD	5	6	5	—	16
Accident	2	1	3	—	6
Infection	3	—	1	—	4
Cardiac failure	1	—	—	—	1
Sudden	2	0	2	1	5
Unknown	3	4	1	—	8
Total	31	13	14	1	59

PVOD = pulmonary vascular obstructive disease.

Mortality: Of the 296 surviving patients, 59 (20%) died from 1 month to 33 years after the operation. The 59 deaths at an average of 26.8 years of follow-up are higher than the 8.64 expected deaths. The standardized mortality ratio and 95% confidence interval are 6.8 (5.1 to 8.7). Thirty-one deaths occurred in the first decade after surgery, 13 in the second, 14 in the third and 1 in the fourth (Figure 1). This equates to 11 deaths/1,000 patient years during the first decade, and 5 deaths/1,000 patient years during the second and third decades after surgery. The year when surgery was performed did not make a difference ($p = 0.3$) on survival. Table I lists the ages at operation for these patients, and the number in each of these age groups who are still living. Age did not seem to be a good predictor, either as a continuous or categorical variable. The age categories <5 and ≥ 5 years provided the best split, with younger children having a better survival early ($p = 0.05$).

Late deaths occurred from a variety of causes (Table II). In 10 patients, death was presumably caused by heart block (7 complete and 3 transient heart blocks after surgery). Only 1 of the latter 3 patients had history of syncope. Eight patients did not receive a cardiac pacemaker, because they were treated in an era before pacemakers were developed. The other 2 patients received a pacemaker, and death occurred presumably from pacemaker failure. Nine other patients died during an operation for a residual cardiac abnormality. They were among 19 patients in whom a cardiac reoperation was performed. In 8 of the 9 patients, death occurred 6 months to 9 years after the initial operation. The ninth patient died 21 years after closure of VSD, after aortic and mitral valve replacements for valvar disease associated with coexistent Marfan syndrome.

Another 16 patients, each with a pre- or postoperative pulmonary resistance >7 mm Hg/liter/min/m^2, died from 2 to 24 years after surgery. Eight of these patients had a major increase in pulmonary vascular resistance after surgery (Figure 2).

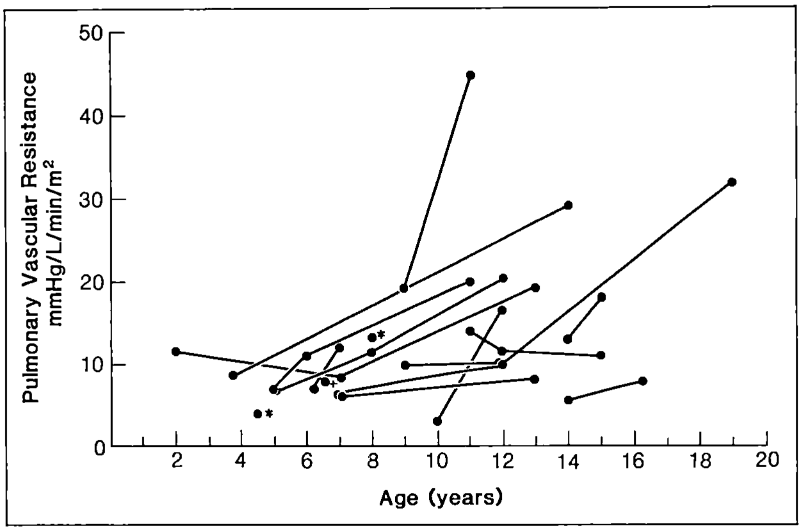

FIGURE 2. Ventricular septal defect after surgery. Pulmonary vascular resistance in 16 patients who died. Pre- and postoperative values connected in 13 patients. *Only preoperative values available in 2 patients; + = only postoperative values available in 1 patient.

Six of the 59 patients died accidentally (2 each from drowning and automobiles, 1 from boating and 1 from a cervical cord injury in a trampoline accident). None of these 6 patients had transient heart block after surgery, and only 1 had an increased pulmonary vascular resistance.

Four patients died of complications of infections. Three were related to complications of infective endocarditis (2 from rupture of an intracranial mycotic aneurysm and 1 from aortic insufficiency). The fourth patient, a 5-year-old, died 3 months after surgery from staphylococcal sepsis. One patient with a residual VSD and a perforation in the septal leaflet of the tricuspid valve died from congestive cardiac failure 3 months after surgery.

TABLE III Ventricular Septal Defect After Surgery: Sudden and Unexpected Deaths (details in 5 patients)

Patient	Age at Death (yrs)	Postoperative Duration (yrs)	Postoperative Electrocardiogram	Block
1	24	3	QRS = 0.18 sec	0
2	11	8	CRBBB	0
3	24	22	CRBBB	0
4	39	29	Normal	Transient
5	38	33	LAD + CRBBB	0

CRBBB = complete right bundle branch block; LAD = left-axis deviation; 0 = absent.

TABLE IV Ventricular Septal Defect After Surgery; Relation Between Pulmonary Vascular Resistance Before Surgery and Late Deaths

Pulmonary Vascular Resistance (mm Hg/L/min/m^2)	No. of Patients	No. of Late Deaths
<3	44	2 (5%)
3–5	45	5 (11%)
5–7	46	8 (17%)
7–10	14	9 (44%)
>10	19	8 (42%)

Five patients died suddenly and unexpectedly with no cardiac symptoms (Table III); 1 died after exercise (patient 1) and another in the postpartum period (patient 2).

Eight other patients, each with a closed defect, died from unknown causes, or the circumstances regarding their deaths could not be fully ascertained. Only 1 of these patients had transient heart block after surgery. The pulmonary vascular resistance was 6 mm Hg/liter/min/m^2 in 1 patient, and normal in the remainder.

In 168 patients, cardiac catheterization data before surgery allowed calculation of the pulmonary vascular resistance (Table IV). Among the 135 patients with pulmonary vascular resistance >7 mm Hg/liter/min/m^2 there were 15 (11%) deaths, whereas in the 33 with pulmonary vascular resistance exceeding this value there were 17 (51%) deaths from all causes, not only from pulmonary vascular disease. In 134 patients (80%), no residual shunt was found during cardiac

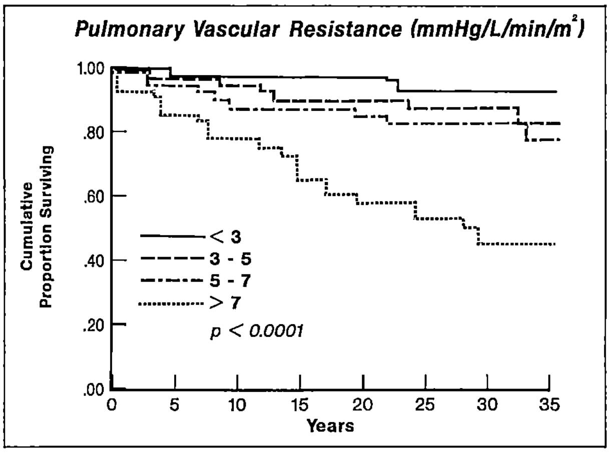

FIGURE 3. Ventricular septal defect after surgery. Life table analysis of 168 patients divided into categories according to level of pulmonary vascular resistance before surgery.

TABLE V Ventricular Septal Defect After Surgery: Type of Conduction Disturbance in 258 Patients

Type of Conduction Disturbance	Status		
	Alive	Dead	Total
None	34	1	35
Right bundle branch block	142	26	168
Right bundle branch block + left-axis deviation	7	2	9
Transient heart block	29	8	37
Complete heart block	2	7	9
Total	214	44	258

catheterization. Pulmonary vascular resistance before surgery (Figure 3) was a significant variable in univariant and multivariant analyses (p <0.001).

Electrocardiographic abnormalities and conduction disturbances Electrocardiographic recordings after surgery, and descriptions of intra- and postoperative events concerning arrhythmias were available for review in 258 patients (Table V). Conduction disturbance was found to be a significant risk factor by univariant and multivariant analyses (p <0.001), with normal conduction being the best situation, complete right bundle branch and transient heart blocks occupying an intermediate position, and the combination of left-axis deviation with complete right bundle branch and complete heart blocks having the highest risk (Figure 4). In 35 patients (13.5%) electrocardiography after surgery was normal, and there were no episodes of postoperative block. Only 1 of these patients died, and that death occurred in an automobile accident. In another 177 patients (68.6%), a pattern of right bundle branch block was present. In 9 of these patients, there was also left-axis deviation Two of these patients had transient block after surgery; both died suddenly, 1 at 14 years and the other at 33 years after surgery.

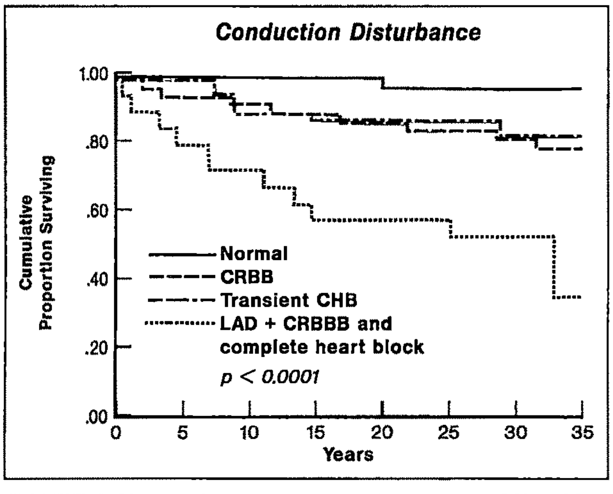

FIGURE 4. Ventricular septal defect after surgery. Life table analysis of 258 patients divided into categories according to type of conduction abnormality after surgery. CHB = complete heart block; CRBBB = complete right bundle branch block; LAD = left-axis deviation.

TABLE VI Ventricular Septal Defect After Surgery: Bacterial Endocarditis (details of 9 episodes in 8 patients)

Years After Surgery	Anatomic Details
4	No defect
4	No defect
7*	Mycotic aneurysm
7*	Mycotic aneurysm
8	Residual VSD
8*	Aortic valve abnormality
19*	Aortic valve abnormality
12 & 21	No defect

*Death.
VSD = ventricular septal defect.

An additional 37 patients (14.3%) had transient heart block during the perioperative period that reverted to normal sinus rhythm within 6 weeks. Of these 37 patients, 29 are living and 8 have died. In 3 of these patients, death was attributed to pulmonary vascular obstructive disease. Two other patients died suddenly after surgery (6 and 14 years, respectively); 1 of these had episodes of syncope. Two other patients died of unknown causes. Only 2 of the 37 patients developed complete heart block after surgery (6 and 25 years, respectively). The remaining 9 of the 258 patients had complete heart block after surgery and 7 have died (described previously). The remaining 2 patients received pacemakers at 7 and 15 years after surgery, respectively.

Arrhythmias: Twenty patients had an arrhythmia after surgery. Eight of these patients had episodes of supraventricular tachycardia, 2 had atrial flutter and 3 had atrial fibrillation. One patient had 1 episode of ventricular tachycardia 23 years after surgery. Another 4 patients had premature ventricular contractions; 3 of these were treated. In the remaining 2 patients, an arrhythmia was reported but not described. Of 13 patients with supraventricular tachyarrhythmia, 5 had a major cardiac residual problem (cardiomyopathy in 2, replacement of either the mitral or tricuspid valve in 1 each, and obstructive pulmonary vascular disease in 1).

Serious illnesses: Nine episodes of infective endocarditis occurred in 8 patients from 4 to 22 years after surgery (Table VI). The rate of occurrence is 11.4/10,000 patient years. Three of these patients died from complications of endocarditis (described previously). In 3 of these patients, cardiac catheterization after surgery showed neither a residual defect nor a shunt. The episodes of endocarditis occurred before echocardiography was available to identify the site of infection.

There were few other serious illnesses among the surviving patients. Five patients developed diabetes mellitus (current ages 34, 40, 40, 55 and 65 years). There is 1 case each of the following conditions: Hodgkin's disease; breast cancer; multiple sclerosis; and rheumatic fever. Two patients have mild restrictive pulmonary disease.

In 3 patients, dilated cardiomyopathy has been diagnosed. Each of these patients developed congestive cardiac failure 20 to 30 years after surgery, and echocardiograms showed ventricular dilatation. Cardiac transplantation is being considered in 2 of these patients. A specific cause for the cardiomyopathy has not been identified.

Exercise status: The surviving patients were asked to rate their exercise ability according to the New York Heart Association criteria. Among the 232 patients, 208 were class 1 and 18 were class 2. Four patients described themselves as class 3 (1 is a patient in a group home, another has gross obesity, the third has severe scoliosis, and the fourth, despite this self-classification, performs manual labor). Two patients were in class 4 (1 with multiple sclerosis and the other with severe developmental delay).

Offspring: Among 294 offspring of the surviving patients, 9 (3%), each from a different family, have congenital cardiac malformation. In 4 offspring, the mother had undergone surgery, and in 5 the father had. In 3 of these 9 offspring there was a VSD, and in 2 others an atrial septal defect. There was 1 case each of atrioventricular septal defect, common arterial trunk, coarctation of the aorta, and pulmonary stenosis.

Cardiac reoperation: In 19 patients (6%), a second cardiac operation was performed; 17 reoperations were performed within the first 10 years (10 primarily for a residual shunt, 2 for tricuspid regurgitation and 1 for an aortic abnormality). In the remaining 2 cases, the aortic valve was replaced at 20 and 21 years, respectively, after the initial operation to close the VSD. As indicated previously, death occurred after 9 of these 19 reoperations.

Educational status: The educational status of 232 surviving patients was ascertained. Twenty-three patients, including 7 in special education classes, did not complete high school. Another 52 patients had no formal education after receipt of a high school diploma. Twenty-five patients attended a technical school after high school. Finally, 132 patients (57%) attended college (44 bachelor degrees [19%], 24 master's degrees [10%] and 12 doctoral degrees [5%] [including 5 physicians]).

DISCUSSION

On March 26, 1954, the first VSD was closed by surgeons at the University of Minnesota Hospital.[1-7] During the next 6 years, a total of 341 patients underwent this operation at our hospital. In this report, we describe the current status of 290 of the 296 postoperative surviving patients. Fifty-nine deaths have occurred among these patients. Deaths have occurred in each decade since the operation, with more occurring during the first 10 years. In analyzing the groups of patients with significantly better survival, there were those who were aged <5 years at surgery, those with lower pulmonary vascular resistance, and those with either normal electrocardiograms after surgery. The survival was better for those who were aged <5 years at surgery ($p < 0.05$). Although intracardiac repair of VSD during infancy is considered a new development, 26 of our patients were aged <2 years at surgery (the youngest aged 4 months). Of these patients, only 3 subsequently died (none from obstructive pulmonary vascular disease). All deaths from obstructive pulmonary vascular disease occurred in patients aged >2 years at surgery.

The effects of elevated pulmonary vascular resistance on survival after VSD closure have been studied,[6-8,12-14] and mortality was found to be greater in patients with a resistance >7[13] or 8[8,12,14] mm Hg/liter/min/m^2. Among our patients, we found a late mortality of 51% for those with preoperative levels >7 mm Hg/liter/min/m^2, and 11% for those with lower levels. The significantly higher mortality was due to not only pulmonary vascular disease but all causes. Pulmonary vascular disease may have been an important factor in the death of patients from other causes. We could attribute only 1 death to obstructive pulmonary vascular disease among patients with low preoperative levels of pulmonary vascular resistance. Because of its unique nature, that case was previously described.[7] Sixteen deaths were attributed directly to obstructive pulmonary vascular disease and its complications. Each of these patients was aged ≥5 years at surgery. The deaths occurred from 2 to 24 years after VSD closure.

Conduction abnormalities have been a major concern in patients after surgery[17-24] and were a significant risk to our patients. Patients with coexistent complete right bundle branch block and left-axis deviation are not considered to develop complete heart block unless transient heart block is present during the perioperative period.[18,21,25,26] Our data support this and provide a longer duration of follow-up. Among our 9 patients with coexistent right bundle branch block and left-axis deviation, 2 had sudden death. One of these patients had transient heart block during surgery.

Heart block after surgery has important implications. Of our 37 patients with transient block after surgery, 2 subsequently developed complete heart block at 6 and 25 years, respectively. Eight of these 37 patients died (3 obstructive pulmonary vascular disease, 2 suddenly and unexpectedly, 2 unknown causes and 1 complete heart block without a pacemaker). Ten other patients with complete heart block have died. Eight of these patients had not received a pacemaker because either pacemakers had not been developed or they were newly available[27,28] and the indications for their use were still being explored. Two of these patients received pacemakers, and died because of pacemaker failure. Our study confirms the serious and life-threatening nature of operatively-induced complete heart block that fortunately is an infrequent complication in the current era of cardiac surgery.

Nineteen patients underwent a second cardiac operation (14 for residual shunt and 2 for significant tricuspid regurgitation). With improvements in operative techniques, a significant residual shunt or tricuspid regurgitation occurs infrequently now. Nine of our 59 deaths occurred after a cardiac reoperation, a situation that would rarely occur today. Another patient who died from congestive heart failure can be considered in the same category, because his death was related to a large residual defect.

Therefore these 36 deaths (10 heart block, 9 cardiac reoperation, 1 heart failure and 16 obstructive pulmonary vascular disease) would largely be avoided with current management principles. The tendency to operate on patients aged <2 years avoids the development of pulmonary vascular disease, and current techniques usually result in complete closure without damage to the conduction system.

Another 13 of our patients died suddenly and unexpectedly or from unknown causes. Another 6 deaths were accidental, a frequent risk for young adults. Four deaths occurred after complications of infection, the risk of endocarditis existing in patients with a cardiac malformation. Thus, whereas we believe the long-term outcome of this group of patients (among the first to undergo open-heart surgery) has been very good we anticipate that the outlook for patients currently undergoing closure of VSD should be excellent.

The health status of our surviving patients is excellent, with few indicating the presence of major medical problems. One concern is the apparent cardiomyopathy in 3 patients. The origin of this cardiac problem is unknown, but may be related to the method of cardioplegia. We have not surveyed our other patients to determine if others who are asymptomatic have similar but less severe echocardiographic changes.

Infective endocarditis occurred in 9 of our patients (11.4/10,000 patient years), a rate similar to the 11.7/10,000 patient years reported in unoperated children aged 2 to 17 years,[29] and to the 12/10,000 patient years reported in children aged 2 to 14 years, some of whom had undergone cardiac surgery.[30] Three of our patients who developed endocarditis had no residual shunt. A previous report described infective endocarditis in patients with successfully closed VSD.[23] This occurrence again emphasizes the recommendation for antibiotic prophylaxis for dental, oral surgical and other procedures in patients with structural cardiac disease. Seven of the episodes of endocarditis that occurred among our patients were during the era before recommendation for antibiotic prophylaxis in patients after surgery.

Another problem after surgery has been the occurrence of arrhythmias in 20 patients, most of whom received treatment (in each case, with 1 medication). In patients with a sustained rhythm disturbance, particularly if unusual (i.e., atrial flutter and fibrillation, and ventricular tachycardia), further investigation is needed.

The incidence of complete closure of VSD in this very early series compares favorably with that in other studies.[10,16,31,32] Despite the major obstacles to cardiac surgery in the 1950s, our operative mortality was only 13%, and the complete closure rate was high (80%). With the improvements in cardiac surgery, the outlook for an infant born today with VSD should be considerably better than that of 35 years ago when this series began.

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Comparison of Transcranial Doppler Ultrasound and Transesophageal Contrast Echocardiography in the Detection of Interatrial Right-to-Left Shunts

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Transesophageal contrast echocardiography is an effective but semiinvasive technique for the detection of interatrial right-to-left shunts. Transcranial Doppler ultrasound is an alternative noninvasive method, but may be limited by false-positive diagnoses due to intrapulmonary shunting. This study examined the accuracy of transcranial Doppler for the detection of shunt lesions. Transcranial Doppler of the right middle cerebral artery was performed simultaneously with transesophageal and transthoracic contrast echocardiography in 32 patients using agitated saline contrast during normal respiration and Valsalva. Transesophageal contrast echocardiography diagnosed an interatrial right-to-left shunt in 13 patients and intrapulmonary shunting in 6 patients. Transcranial Doppler identified all 13 interatrial right-to-left shunts and an intrapulmonary shunt in 3 of 6 patients. Absence of a shunt was confirmed by transcranial Doppler in 12 of 12 patients. Transcranial Doppler had a sensitivity of 100% (13 of 13), specificity of 100% (18 of 18) and accuracy of 100% (31 of 31) for prediction of an interatrial right-to-left shunt by transesophageal contrast echocardiography. In comparison, transthoracic contrast echocardiography had a sensitivity of 54% (7 of 13), specificity of 94% (17 of 18) and accuracy of 77% (24 of 31). Thus, transcranial Doppler is highly accurate for detection of an interatrial right-to-left shunt and not compromised by physiologic intrapulmonary shunts, whereas transthoracic contrast echocardiography lacks sensitivity. Transcranial Doppler may be useful as an alternative to transesophageal study, where the primary indication for transesophageal echocardiography is exclusion of an interatrial right-to-left shunt.

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In patients with unexplained cerebral ischemic events, echocardiography is increasingly used to detect possible cardiac sources of thromboembolism and to identify interatrial right-to-left communications. The latter may serve as a mechanism of paradoxic embolism,[1–3] and identification of such lesions may allow for definitive treatment.[3–5] Contrast echocardiography has been used to detect such communications.[6,7] However, transthoracic contrast echocardiography is limited by inadequate imaging, especially during provocative maneuvers (e.g., Valsalva) designed to enhance right-to-left shunting of contrast. Transesophageal contrast echocardiography facilitates undisturbed imaging during contrast studies, with a commensurate improvement in sensitivity,[8] but has the disadvantage of semi-invasiveness and limited availability.

Transcranial Doppler ultrasound examination of the middle cerebral artery during contrast injection is a noninvasive technique which has recently been reported to improve the sensitivity of transthoracic echocardiography for the detection of an interatrial right-to-left shunt.[9] However, this technique may be limited by false-positive diagnoses due to intrapulmonary shunting, which has been documented in normal subjects by transesophageal contrast echocardiography.[10] This study examined the accuracy of transcranial Doppler for detecting interatrial shunts after contrast injection using simultaneous transesophageal and transthoracic echocardiographic imaging.

METHODS

Patients: Between March 1990 and November 1990, 32 patients underwent transthoracic and transesophageal contrast echocardiography in conjunction with transcranial Doppler examination of the right

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middle cerebral artery. The study group consisted of 14 men and 18 women aged 22 to 78 years (mean 50). Echocardiography was performed in 21 patients because of unexplained cerebral or peripheral vascular ischemic events (19 cerebrovascular strokes, 1 cerebral transient ischemic attack and 1 renal infarct). The remaining 11 patients underwent echocardiographic evaluation for unrelated reasons. Cardiac or cerebrovascular disease was present in 14 patients (44%), and 18 (56%) were free of identifiable disease as assessed by history, physical examination, electrocardiogram, chest roentgenogram, and carotid duplex ultrasound or cerebral angiographic studies. Coronary artery disease was present in 7 patients (22%), atrial fibrillation in 3 (9%), and valvular disease in 9 (28%).

Echocardiographic protocol: Each patient was brought to the echocardiographic laboratory after a 6-hour fast. Standard transthoracic and transesophageal[11] echocardiographic examinations using commercially available machines were performed using 2-dimensional, Doppler and color Doppler evaluations. Imaging after contrast injection was performed during normal respiration and Valsalva maneuver.

Contrast studies were performed using a mixture of 6 ml of saline solution, a small volume (0.5 ml) of air, and a drop of the patient's blood. This mixture was vigorously agitated by pumping between two 10 ml syringes connected by a 3-way stopcock and then immediately injected via a catheter into an antecubital vein.[9]

An interatrial right-to-left shunt was diagnosed if contrast crossed the interatrial septum within 1 to 2 cardiac cycles after its appearance in the right atrium. Intrapulmonary shunting was diagnosed by delayed appearance of contrast in the left cardiac chambers. Findings were considered indeterminate if the presence or absence of contrast appearing in the left cardiac chambers was not definite or the timing of contrast appearance was unable to be determined.

Transcranial Doppler examination: A 2 MHz transcranial pulsed Doppler transducer (Medasonics Transpect, Mountain View, California) was positioned so as to obtain flow of the right middle cerebral artery during the transthoracic and transesophageal contrast echocardiographic examinations.[9] Transcranial Doppler was considered positive for a right-to-left shunt if 1 or more contrast microcavitations were detected in the Doppler flow signal after contrast injection. The signals produced by the contrast microcavitations were characterized by a distinctive auditory finding that had a high-pitched "popping" quality. Microcavitations produced 2 distinct patterns in the transcranial Doppler flow signal, which was recorded on a strip-chart recorder. Isolated microcavitations, which had a high fluid-to-air acoustical impedance ratio, were manifested by increased brightness which tracked the velocity of surrounding red blood cells. Large numbers of microcavitations saturated the amplifier and software causing transient interruption of the Doppler signal on the tracing (Figure 1). However, this did not result in interruption of the auditory signal, which was characterized by repetitive popping auditory signals. The audio signal output was passed through a zero crossing counter which was connected to an auxiliary port of the echocardiographic machine. This enabled the Doppler audio signal and a waveform envelope to be recorded on the same ½-inch VHS videotape used to record the echocardiographic images (Figures 2 and 3).

Statistical analysis: The results of transcranial Doppler and contrast echocardiography were interpreted for 3 groups of patients: those with an interatrial right-to-left shunt, those with physiologic intrapulmonary shunts, and those without evidence of a shunt. Using transesophageal contrast echocardiography for comparison, the sensitivity, specificity and accuracy of transcranial Doppler and transthoracic contrast echocardiography for prediction of an interatrial right-to-left shunt were assessed. Sensitivity was calculated as the percentage of patients with a shunt identified as

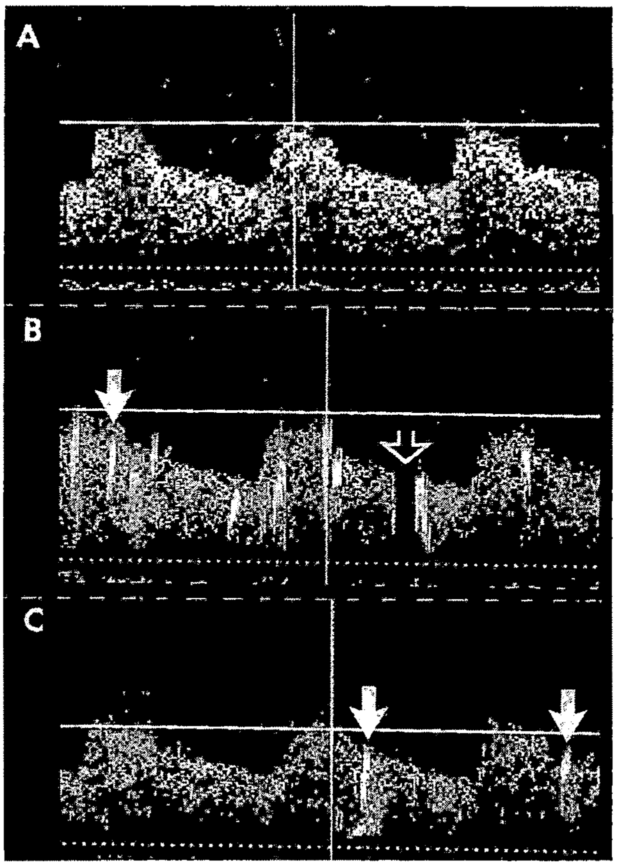

FIGURE 1. Transcranial Doppler ultrasound recordings of middle cerebral artery blood flow. *A*, normal flow pattern before contrast injection; *B and C*, patterns seen in the presence of an interatrial *(B)* and intrapulmonary *(C)* shunt illustrating detection of isolated *(closed arrows)* and numerous *(open arrow)* microcavitations, the latter of which interrupt the flow signal.

true positives. Specificity was calculated as the percentage of patients without a shunt confirmed as true negatives. Accuracy was calculated as the percentage of patients with and without shunts identified correctly.

RESULTS

Transesophageal contrast echocardiography: Transesophageal contrast echocardiography identified the presence of an interatrial right-to-left shunt in 13 patients: 11 with an intact interatrial septum and 2 with an atrial septal defect (1 being secundum and the other sinus venosus in type). Right-to-left shunting of contrast was present in 11 patients during normal respiration, whereas shunting occurred only during Valsalva maneuver in 2 patients. In each case, multiple contrast microcavitations crossed the interatrial septum within 1 to 2 cardiac cycles (Figure 2). Both patients with an atrial septal defect demonstrated a right-to-left shunt. A single patient failed to show right-to-left contrast shunting but had left-to-right shunting across the interatrial septum on color Doppler and negative contrast effect in the right atrium, presumably representing a small atrial septal defect despite an intact septum on 2-dimensional imaging. Intrapulmonary shunting was identified in 6 patients and manifested by only a few contrast microcavitations which had a delayed appearance in the left atrium (Figure 3). No evidence of a shunt was found in the remaining 12 patients.

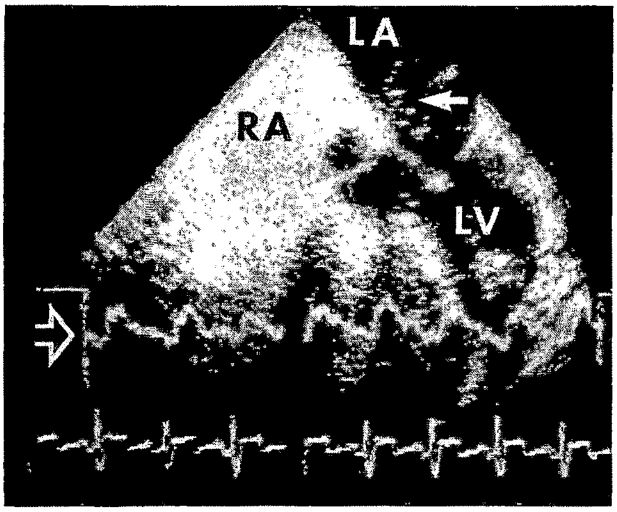

FIGURE 2. Transesophageal 4-chamber image illustrating passage of contrast microcavitations *(closed arrow)* across the interatrial septum in the presence of an interatrial shunt. Transcranial Doppler waveform envelope is depicted in lower portion of figure *(open arrow)*. LA = left atrium; LV = left ventricle; RA = right atrium.

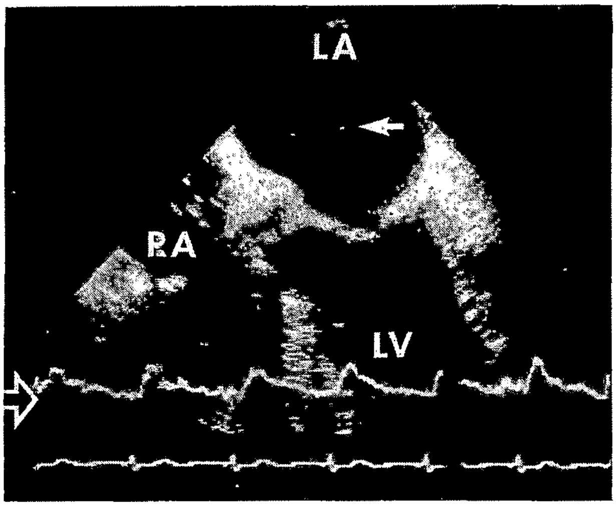

FIGURE 3. Transesophageal 4-chamber image illustrating late appearance of a contrast microcavitations in left atrium (LA) in the presence of an intrapulmonary shunt. Note that the echocardiographic contrast has essentially cleared from the right atrium (RA) by this time. LV = left ventricle.

Transthoracic contrast echocardiography: Transthoracic contrast echocardiography identified the presence of an interatrial right-to-left shunt in 7 of the 13 patients (54%) identified by transesophageal echocardiography. Additionally, 4 patients had indeterminate studies. Both patients with an atrial septal defect identified by transesophageal echocardiography were identified by transthoracic contrast echocardiography and exhibited a right-to-left shunt. The single patient with only a left-to-right shunt by transesophageal echocardiography had no evidence of an interatrial shunt on transthoracic examination either by contrast techniques or color Doppler. Evidence of intrapulmonary shunting observed in 6 patients by transesophageal contrast echocardiography was not identified by transthoracic contrast echocardiography. Of the 12 patients without evidence of a shunt by transesophageal echocardiographic examination, 11 were identified correctly and the remaining study was indeterminate by transthoracic echocardiography. This produced an overall sensitivity of 54% (7 of 13), specificity of 94% (17 of 18) and accuracy of 77% (24 of 31) for detection of an interatrial right-to-left shunt by transthoracic contrast echocardiography (Figure 4).

Transcranial Doppler: Transcranial Doppler detected multiple microcavitations after right-to-left shunting of contrast in all 13 patients (100%) with an interatrial right-to-left shunt identified by transesophageal echocardiography, including both patients with an atrial septal defect. The single patient who only manifested left-to-right flow on color Doppler and negative contrast effect in the right atrium during transesophageal echocardiography had no detectable microcavitations. Of the 6 patients with intrapulmonary shunts identified by transesophageal echocardiography, transcranial Doppler detected only a few microcavitations in 3 patients and none in the remaining 3 patients. The 12 patients (100%) without any evidence of a shunt by transesophageal echocardiography had no microcavitations detected by transcranial Doppler.

Transcranial Doppler was able to distinguish interatrial right-to-left shunts from intrapulmonary shunts based on the quantity of microcavitations which were shunted. The distinct audio quality and recorded patterns of detected microcavitations allowed for quantitation (Figure 1). Interatrial shunts were characterized by ≥ 5 microcavitations (usually these were too numerous to count). Intrapulmonary shunts, however, were characterized by <5 or no detectable microcavitations (no patient with an intrapulmonary shunt had >3 microcavitations). With use of these parameters, transcranial Doppler was able to predict the presence of an interatrial right-to-left shunt with a sensitivity of 100% (13 of 13), specificity of 100% (18 of 18) and accuracy of 100% (31 of 31) (Figure 4).

DISCUSSION

This study demonstrates that transcranial Doppler is highly accurate for the detection of right-to-left shunts and that intrapulmonary shunting does not result in false-positive diagnoses. Transcranial Doppler improved the ability of transthoracic contrast echocardiography to detect interatrial right-to-left shunts and clarified indeterminate and false-negative transthoracic studies.

Transthoracic contrast echocardiography: Several reports have noted an association between the presence of an interatrial right-to-left shunt and embolic cerebral and peripheral vascular events.[1-5] Transthoracic contrast echocardiography is able to detect very small right-to-left shunts.[6] Provocative maneuvers, such as Valsalva and cough, have been used to improve the sensitivity of the technique by enhancing the degree of right-to-left shunting. Kronik and Mosslacher[12] reported that $>90\%$ of patients with an atrial septal defect and 64% of patients with a patent foramen ovale had contrast studies positive for a right-to-left shunt. Dubourg et al[7] found the sensitivity of contrast echocardiography for detection of an interatrial right-to-left shunt during normal respiration to be only 40%, but this increased to 60% with Valsalva and to 100% with cough. Specificity remained at 78% for all 3 methods. The results of the present study using transthoracic contrast echocardiography with Valsalva are in accord with these findings.

Transesophageal echocardiography in diagnosis of interatrial shunt: Transesophageal echocardiography affords improved ability to detect intracardiac sources of emboli. Furthermore, because it offers undisturbed imaging, transesophageal contrast echocardiography has been found to be highly accurate in detecting interatrial right-to-left shunts.[8] In comparison, transthoracic contrast echocardiography is limited by inadequate and, at times, loss of imaging, particularly during provocative maneuvers designed to increase its sensitivity.

Doppler techniques: Previous studies have reported the ability of Doppler techniques to detect air emboli[13] and saline contrast microcavitations.[14] More recently, transcranial Doppler has enabled detection of air emboli during carotid endarterectomy.[15] Teague and Sharma[9] found that transcranial Doppler improved the accuracy of transthoracic contrast echocardiography for detection of interatrial right-to-left shunts, particularly when studies were indeterminate. However, the issue of whether intrapulmonary shunting could create false-positive diagnoses was not evaluated. Wittlich and Kramer[10] documented intrapulmonary shunting of contrast in all 24 of their normal subjects by transesophageal echocardiography using agitated gelatine solution. Although intrapulmonary shunting of contrast was also observed in our study, its prevalence was low and the degree of this shunting was of small magnitude or not detectable. The ability to quantitate the shunted microcavitations permitted differentiation between interatrial and physiologic intrapulmonary shunts. The prevalence and magnitude of intrapulmonary shunting may be due to the type of echocardiographic contrast agent used:

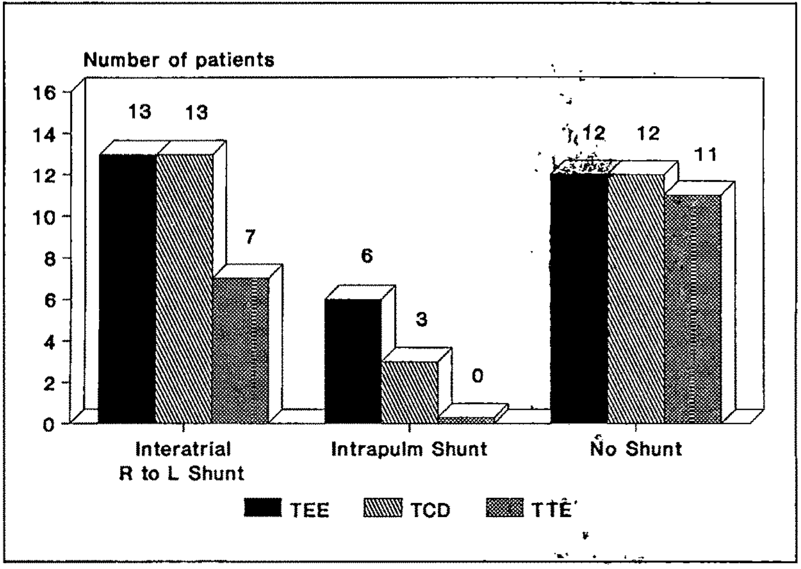

FIGURE 4. Comparison of transesophageal echocardiography (TEE), transcranial Doppler ultrasound (TCD) and transthoracic echocardiography (TTE) in detecting various types of shunts. L = left; R = right.

Wittlich and Kramer used agitated gelatine solution, whereas the present study used agitated saline mixed with air and blood. These different methods result in different contrast microcavitation bubble diameter, with more viscous solutions producing smaller diameter microbubbles that are able to undergo transpulmonary passage and cause positive transcranial Doppler signals.[16] Although this issue was not analyzed in the present study, gelatine-based contrast is reported to produce microbubbles measuring 12 ± 10 μ in diameter,[16] whereas the method of producing saline contrast used in this study gives bubbles of 24 to 180 μ.[9] The admixture of blood to saline produces a more viscous solution and facilitates transpulmonary passage of microcavitations in comparison with standard saline contrast.

The use of carotid Doppler ultrasound to detect shunted contrast microcavitations has not been reported and warrants further investigation. If this technique were to prove as efficacious as transcranial Doppler in detecting contrast microcavitations, then it would represent a method more frequently available for use in conjunction with contrast transthoracic echocardiography.

Study limitations: This study compared results of transcranial Doppler with transesophageal and transthoracic echocardiography. The design did not include independent confirmation of the echocardiographic findings with the exception of the 2 atrial septal defects, both of which were confirmed surgically. However, previous studies have documented the accuracy of echocardiographic techniques in detecting patent foramen ovale by surgical, pathologic and catheterization techniques.[3,6]

Transcranial Doppler techniques have previously been used to detect air emboli and saline contrast microcavitations.[9,15] We believe that the temporal relation of the detection of microcavitations after contrast injection in this study, and their absence before injection, confirms the observed characteristics of the changes in the transcranial Doppler waveform. Transcranial Doppler techniques are limited in detecting right-to-left shunts; this is demonstrated in the present study by the single patient with an interatrial left-to-right shunt by transesophageal echocardiography.

Clinical role of transcranial Doppler: Transcranial Doppler may be useful as an alternative to transesophageal echocardiographic study in selected patients for whom the primary indication for transesophageal study is exclusion of an interatrial right-to-left communication. The efficacy of carotid Doppler ultrasound in detecting shunted microcavitations warrants further investigation, since this technique would be available more often than transcranial Doppler ultrasound.

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Effect of Digoxin on ST-Segment Changes Detected by Ambulatory Electrocardiographic Monitoring in Healthy Subjects

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Digoxin causes false-positive ST depression during exercise stress testing, but it is unknown if digoxin produces ST depression during ambulatory electrocardiographic monitoring. Fifty healthy volunteers underwent both exercise stress testing and ambulatory electrocardiographic monitoring before and after 14 days of digoxin (0.25 mg/day) administration. Significant ST depression was defined as ≥1 mm of horizontal or downsloping ST depression 80 ms after the J point lasting for ≥60 seconds.

During therapy, 13 subjects (26%) had at least 1 episode of ST depression and 5 subjects (10%) had multiple episodes of ST depression detected by ambulatory monitoring. Ten subjects (20%) had ST depression that occurred during exercise that was detected by both stress test and ambulatory monitoring. Three subjects (6%) had ST depression that was detected on the ambulatory recording only at times other than during the stress test. Stratification of demographic and clinical variables did not predict digoxin-induced ST depression.

Thus, digoxin causes false-positive ST depression detected by ambulatory monitoring. The incidence is similar to that observed during stress testing, but also occurs at heart rates lower than that achieved during stress tests. Ambulatory electrocardiographic monitoring will be less useful in the noninvasive assessment of coronary artery disease in patients receiving digoxin.

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Ambulatory electrocardiographic monitoring is being used to document episodes of ST-segment depression occurring with or without associated symptoms of myocardial ischemia.[1,2] The frequency and severity of ST-segment depression detected by ambulatory monitoring correlates well with clinical outcome in selected patient groups.[3,4]

Digitalis glycosides are known to produce false-positive ST-segment depression during exercise stress testing in both normal subjects and patients with coronary artery disease.[5–8] It is not known if digoxin-induced false-positive ST-segment depression occurs during ambulatory monitoring. The purpose of this study was to determine whether digoxin induces ST-segment depression during ambulatory monitoring. In addition, this study examined the concordance of digoxin-induced ST-segment depression observed during ambulatory monitoring and upright treadmill exercise stress testing.

METHODS

Subjects: We studied 60 healthy men between the ages of 21 and 37 years of age (mean 29 ± 4). All subjects were nonsmokers and were considered healthy on the basis of a prestudy evaluation that included a history and physical examination, 12-lead electrocardiogram and routine laboratory tests.

The study was approved by our university's institutional review board. All volunteers gave written informed consent before participation in the study.

Protocol: An ambulatory electrocardiographic monitor (Delmar Avionics model 447) was placed and activated before the initial exercise study. Frequency range for this AM recorder was 0.05 to 100 Hz. A 2-lead system with meticulous skin preparation and electrode placement was used. Subjects kept a detailed diary, recording activities and symptoms during the 24-hour recording period. None of the subjects had ST changes with position, hyperventilation or Valsalva maneuver.

After placement of the ambulatory monitor, subjects underwent an upright continuous, multistage Bruce protocol treadmill exercise stress test to 85% of predicted maximal heart rate. The immediate postexercise electrocardiogram was recorded with the subjects

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TABLE I Number of Subjects with ST Depression After Exercise Treadmill Stress Testing

		Subjects (n)			
ECG Lead	ST Depression (mm)	Immediately After Exercise	<1 Min. After Exercise	1–2 Min. After Exercise	2–4 Min. After Exercise
II	1.0–1.9	2	3	0	0
II	2.0–2.9	1	2	1	1
aVL	1.0–1.9	2	2	0	0
V_3	1.0–1.9	3	3	2	0
V_3	2.0–2.9	0	1	0	0
V_4	1.0–1.9	1	1	1	0
V_5	1.0–1.9	6	8	4	2
V_5	2.0–2.9	2	2	1	0
V_6	1.0–1.9	1	4	2	1

ECG = electrocardiographic.

in the standing position, while all other postexercise recordings were obtained in the supine position.

After the 24-hour ambulatory monitoring period was completed, subjects took digoxin (Lanoxin, Burroughs-Wellcome) 0.25 mg/day in the morning for 14 days. On the 14th day of digoxin treatment, subjects returned for a repeat 24-hour ambulatory recording and a Bruce protocol exercise study. A blood sample for determination of serum digoxin concentration was also obtained.

Subjects developing digoxin-induced ST depression during exercise stress returned 7 days after digoxin discontinuation for a third ambulatory recording and Bruce protocol exercise stress test.

Exercise stress tests: Exercise studies were conducted using a Quinton treadmill (model 55) and Quinton (series 5000) recorders. ST depression was considered significant if it occurred in 1 or more postexercise leads (except aVR) and manifested as ≥1 mm of flat or downward sloping ST-segment depression of ≥80 msc duration.

Ambulatory electrocardiographic recordings: Tape recordings were reviewed using a Cardio-Data Prodigy scanner at 120 times real time. Significant ST depression was defined as ≥1 mm of horizontal or downsloping ST depression 80 ms after the J point lasting for ≥60 seconds. Only episodes of ST depression agreed on by 2 reviewers were considered significant. These reviewers were unaware of the results of the exercise studies and treatment with digoxin. Episodes of ST elevation and alternating T-wave polarity were documented. Episodes of ST depression were tabulated noting total duration in minutes, maximal magnitude in millimeters, and time of day and heart rate at onset in beats per minute.

Serum digoxin concentration: Digoxin concentrations were measured by radioimmunoassay using a commercial ^{125}I-RIA-kit (New England Nuclear) after extraction of digoxin with dichloromethane. The lower limit of detection of this assay was 0.5 ng/ml.

RESULTS

Fifty of the 60 subjects successfully completed the study. Four subjects completed the initial evaluation and baseline stress test and ambulatory monitoring, but failed to return for repeat studies. Six other subjects completed the necessary studies, but recorder failures occurred during one of the test periods. Data from these 10 subjects were not included in the analysis.

None of the subjects had ST depression during the initial predigoxin stress tests and 24-hour ambulatory recordings. No subject reported symptoms in their diaries, nor did any subject complain of any adverse effect related to digoxin.

Exercise stress tests: During digoxin treatment, 10 of the subjects (20%) had ST depression during exercise stress. Of these 10 subjects, 7 had ST depression immediately after exercise, 2 had ST depression at 1 minute after exercise and 1 had ST depression at 2 minutes after exercise. Of the 7 patients who had ST depression immediately after exercise, 5 had normalized at 1 minute after exercise and the other 2 had normalized at 2 minutes after exercise. The ST-segments normalized by 4 minutes after exercise in the 3 subjects who had late onset of ST depression. Nine of the 10 subjects had ST depression in >1 lead (Table I).

Ambulatory electrocardiographic monitoring: During digoxin administration, 13 (26%) subjects developed at least 1 episode of ST depression during ambulatory monitoring (Table II). Six of the subjects had ST depression only during the stress test. Four subjects had episodes of ST depression during both the stress test and at other times during the ambulatory recording period. Three subjects had episodes of ST depression only at times other than during the stress test (Figure 1). Concordance between exercise stress and ambulatory monitoring was observed in 10 of the 13 subjects.

Follow-up studies: Follow-up stress tests and ambulatory recordings were obtained 7 days after discontinuation of digoxin in the 10 subjects with stress tests interpreted as showing ischemic ST changes. Three subjects with ST changes detected on ambulatory monitoring but not during exercise stress did not have follow-up studies obtained. Of the 10 subjects with follow-up studies, 4 had ST depression on ambulatory monitoring, the exercise test or both. Two had ST depression on both the stress test and the ambulatory recording, 1 had ST depression only during the exercise test, and 1 had ST depression only during the ambulatory recording.

Digoxin was associated with other electrocardiographic abnormalities detected during ambulatory monitoring including T-wave inversion in 10 subjects (20%) and Mobitz type I second-degree atrioventricular heart block in 5 subjects (10%). These changes were not associated with symptoms.

Serum digoxin concentrations: Serum digoxin concentrations were in the therapeutic range of 0.8 to 2.1 ng/ml in 46 of the 50 subjects (92%). In 3 subjects, digoxin concentrations were <0.8 ng/ml and in 1 subject the digoxin concentration was 2.2 ng/ml. The mean serum digoxin concentration at the time of the exercise test was 1.35 ± 0.44 ng/ml. The digoxin concentrations were <0.5 ng/ml in all 10 subjects who underwent follow-up studies 7 days after digoxin discontinuation.

Serum digoxin concentrations were not significantly different in the 13 subjects with ST depression during ambulatory monitoring as compared with the entire group of subjects or between the 10 subjects with ST depression during exercise tests and the entire group of subjects.

Other predictive factors: There were no significant differences between subjects developing ST depression with digoxin and those who did not with regard to age (<30 vs >30 years), serum creatinine, calculated creatinine clearance, serum potassium, serum magnesium, body surface area, or a positive family history of cardiovascular or coronary artery disease.

DISCUSSION

Ambulatory electrocardiographic monitoring has been used to detect transient ST changes in patients with coronary artery disease. There is evidence that in selected groups of patients, ST depression detected by ambulatory monitoring represents myocardial ischemia.[1,2] Many of these episodes of ST depression are asymptomatic. In certain subgroups of patients with known coronary artery disease, the presence of asymptomatic ST depression has important prognostic implications.[3,4]

Several studies have demonstrated that digoxin can induce ST depression mimicking ischemia during exercise stress testing.[5-8] It has been assumed, but never tested, that digoxin would induce similar changes during ambulatory monitoring. Thus, most studies using ambulatory monitoring as a diagnostic and prognostic tool have excluded patients treated with digoxin.[1-4]

Our study in healthy subjects demonstrates that digoxin induces ST depression that could be interpreted as ischemia. Digoxin-induced ST depression was observed in 26% of subjects during ambulatory monitoring which is similar in frequency to that reported in exercise studies.[5-8] It is interesting to note that in 3 subjects (6%), ST depression did not occur during stress but only at lower heart rates. In addition, ST depression occurred in 7 subjects at times other than during the exercise stress test.

Our study has several limitations. It is possible that spontaneous variation accounted for some of the epi-

TABLE II Severity and Duration of Digoxin-Induced ST-Segment Depression During Ambulatory Electrocardiographic Monitoring

Pt. No.	No. of ST Episodes	Duration of Episodes (min:sec)	Total ST Depression Time (min:sec)	HR at Onset (beats/min)	Maximal Magnitude of ST Depression (mm)	Time of Day
1	2	9:00	14:50	160	1.75	0721
		5:50		98	1.25	1629
2	1	4:30	4:30	162	2.00	0830
3*	3	11:22	31:79	111	1.80	1100
		11:57		84	2.50	1546
		9:00		102	2.10	2107
4	1	8:30	8:30	167	3.70	1004
5	1	6:33	6:33	132	1.80	0730
6	1	8:02	8:02	148	1.40	1005
7	5	6:05	36:19	108	1.35	0815
		5:11		90	2.00	2105
		7:50		86	1.25	2210
		6:12		84	1.35	2230
		11:01		90	1.25	2250
8	1	3:34	3:34	135	2.10	0730
9*	3	7:05	23:39	112	3.60	1519
		8:00		82	1.90	1033
		8:34		80	3.10	1340
10*	1	13:35	13:35	108	4.88	1035
11	1	2:50	2:50	122	1.25	0930
12	1	3:01	3:01	120	1.38	1245
13	4	7:13	27:53	154	2.75	0910
		9:15		100	1.25	1340
		2:50		94	1.15	1745
		8:35		90	1.88	0030

*Subjects with ST-segment depression occurring only at times other than during the exercise stress test.
HR = heart rate.

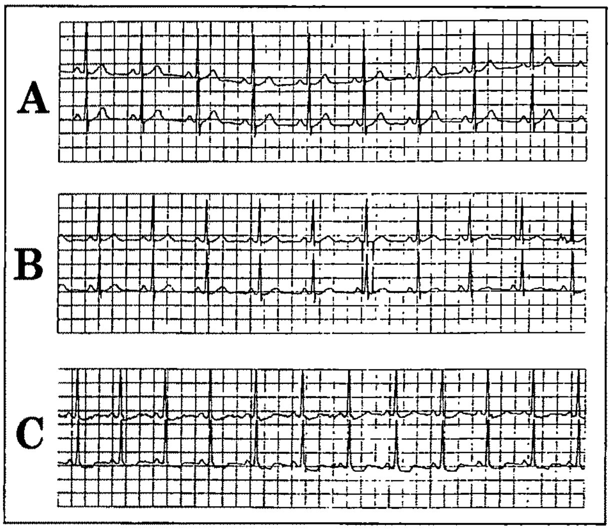

FIGURE 1. Electrocardiographic recording from a single volunteer before ingestion of digoxin *(A)*, during treatment with digoxin at a time of normal ST-segment response *(B)*, and during treatment with digoxin at a time of ST-segment depression occuring with normal daily activity *(C)*.

sodes of ST depression that were attributed to digoxin.[9,10] ST depression has been reported in apparently healthy persons.[11] A longer period of baseline monitoring may have more accurately defined the incidence of spontaneous ST depression in our subjects. However, the incidence of spontaneous ST depression occurs in <3% of healthy subjects and has not been reported in subjects <40 years.[11]

A longer digoxin washout period before repeating follow-up studies in our subjects with ST depression would have provided more convincing evidence that ST depression was digoxin-induced. Repeat studies at 1 week after stopping digoxin in the present study demonstrated ST depression in 4 subjects. Although the digoxin levels were <0.5 ng/ml in these subjects, the pharmacodynamic effects of the drug could have still been present. Previous work at our center has shown that digoxin-induced ST depression normalizes after a 12-day digoxin washout.[5] However, ST depression persists in about 20% of subjects after a 7-day washout.

Last, extrapolation of our study's findings to women, the elderly, or to patients with coronary artery disease should be made with caution. The incidence of digoxin-induced ST depression should be based on studies conducted specifically in these patient populations.

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Two-Dimensional Contrast Echocardiography in the Detection and Follow-Up of Congenital Pulmonary Arteriovenous Malformations

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Pulmonary arteriovenous (A-V) malformation is frequently a manifestation of Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia). We identified 14 patients (9 men and 5 women) with A-V malformation by contrast echocardiography; 10 patients with atrial right-to-left shunt served as control subjects. Agitated saline solution (10 ml) was injected through a peripheral vein during echocardiographic imaging. The delay in the appearance of microcavitations in the left atrium was measured (in number of frames) after right atrial appearance. The degree of left ventricular opacification was graded 1 to 4+ (where 4+ = intense left ventricular endocardial outline, and 1+ = minimal opacification). Results indicated patients with A-V malformation had a significant delay ($p < 0.001$) in left atrial appearance of microcavitations compared with those with atrial right-to-left shunt (66 ± 27 vs 21 ± 7 frames, mean ± 1 standard deviation). In the group with A-V malformation, abnormal blood gases were present in only 6 of 14 patients and chest x-ray was positive in 7. Pulmonary angiography was performed in 11 of 14 patients with positive contrast echocardiography, and all 11 had A-V malformation identified. In patients with 3 to 4+ left ventricular opacification (n = 8), large (>5 mm feeding vessel) or multiple malformations were present, whereas patients with small or isolated malformation had 1 to 2+ left ventricular opacification. Balloon occlusion of malformations was performed in all 11 of these patients; repeat contrast echocardiography revealed significant diminution of right-to-left shunt in 9, and 2 required repeat embolotherapy for an additional previously undetected A-V malformation. Thus, contrast 2-dimensional echocardiography is extremely sensitive for the identification of pulmonary A-V malformation.

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The diagnosis of congenital pulmonary arteriovenous (A-V) malformation associated with hereditary hemorrhagic telangiectasia may be unsuspected, particularly when clinical signs of dyspnea, epistaxis or hypoxemia at rest are not present.[1-3] Typically, confirmation of the diagnosis of pulmonary A-V malformation necessitates pulmonary angiography.[4-6] Early reports described the use of contrast M-mode echocardiography to detect pulmonary A-V malformation.[7-10] After peripheral intravenous injections of agitated saline solution, microcavitations are seen in the left atrium and ventricle after a predictable delay. Two-dimensional echocardiography has major advantages over M-mode techniques and provides direct visualization of the site of appearance of the contrast agent. We studied the accuracy of contrast 2-dimensional echocardiography for the detection of pulmonary A-V malformation and compared the results with those obtained in patients with intraatrial right-to-left shunt. We also examined use of this technique for follow-up of patients with pulmonary A-V malformation after embolotherapy.

METHODS

The study group consisted of 29 patients (17 men and 12 women). Nineteen patients had phenotypic Osler-Weber-Rendu syndrome. Four patients were index cases (i.e., they were known to have Osler-Weber-Rendu syndrome and were suspected to have pulmonary A-V malformation on the basis of radiography or clinical presentation). Fifteen patients were first-degree relatives of the index cases. They were diagnosed consecutively as they presented for screening. Ten patients with atrial right-to-left shunt due to patent foramen ovale (n = 8) or secundum atrial septal defect (n = 2) who had been previously studied were used as control subjects. Patients with patent foramen ovale exhibited

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marked bowing of the intraatrial septum, and those with atrial septal defects had easily identified defects from the subcostal views. All patients underwent standard 2-dimensional echocardiography, including parasternal, apical and subcostal views. In each patient, a peripheral intravenous line (19 gauge butterfly) was established in an antecubital vein, and 2 to 10 ml syringes were connected by a 3-way stopcock. One syringe contained 10 ml of saline solution; a small amount of air (0.2 ml) was introduced into the other syringe. After agitating the saline solution for 10 seconds, a forceful hand injection was performed with simultaneous 2-dimensional imaging in an apical 4-chamber view.

Contrast 2-dimensional echocardiograms were analyzed for the time delay (in frames) between appearance of microcavitations in the left atrium and initial appearance in the right atrium. Relative opacification of the left ventricle was qualitatively assessed on a scale of 1 to 4+. Evidence of minimal left ventricular microcavitations was graded 1+, moderate microcavitations 2+, extensive microcavitations without outlining the endocardium 3+ and extensive microcavitations with clear endocardial definition 4+. Heart rate was measured as the RR interval in milliseconds.

In each of the patients with pulmonary A-V malformation detected by contrast 2-dimensional echocardiography, the following clinical information was obtained from the patient record: presence and location of a bruit; evidence of telangiectasia; history of epistaxis or dyspnea; and history of neurologic events including cerebral abscess and vascular accident, transient ischemic attack and parasthesias in the extremities. Partial pressure of oxygen in the arterial blood at rest was measured, and the standard chest x-ray was reviewed for radiologic evidence of A-V malformation.

In all but 3 patients, diagnostic pulmonary angiography was performed to confirm presence, number and size of malformations. Pulmonary angiography was performed as a clinical diagnostic procedure in patients suspected to have pulmonary A-V malformation. This suspicion was based on symptomatology, radiography, positive echocardiogram, or abnormal room air or 100% arterial blood gases, as well as certain clinical syndromes suggesting that occult pulmonary A-V malformation might be present (i.e., stroke or brain abscess). Informed consent was obtained. Pulmonary angiography was performed with standard 6 and 7Fr pigtail catheters that were introduced into the right femoral vein using the Seldinger technique. The catheter was advanced into the left and right main pulmonary arteries with selective catheterization of pulmonary arterial branches with suspected A-V malformations. Standard cut film angiography was performed; digital subtraction angiography was also performed to supplement these angiograms, as necessary. In all patients with A-V malformation, size of the feeding vessel

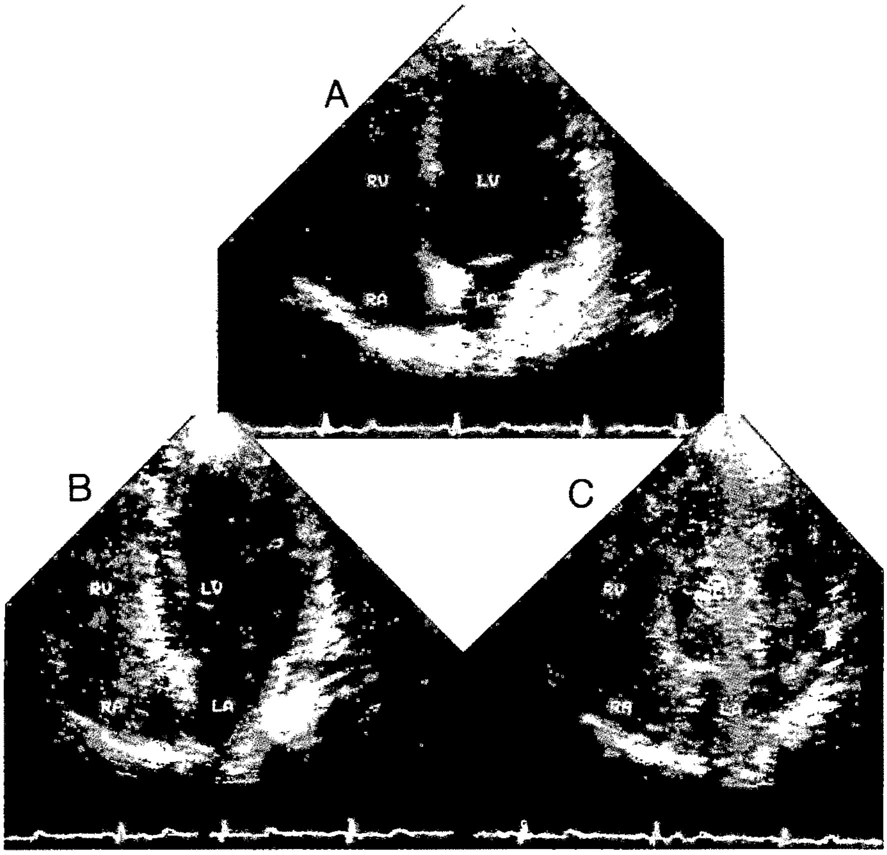

FIGURE 1. ***A,*** **apical 4-chamber view before contrast injection.** ***B,*** **same view after right atrial (RA) and ventricular (RV) opacification, with microcavitations evident in left atrium (LA) and ventricle (LV) after delay of 38 frames.** ***C,*** **same view approximately 5 seconds later demonstrating 4+ opacification of left ventricle.**

supplying the malformation was measured in millimeters. Malformations with feeding vessels >3 mm were embolized using appropriately sized balloons or coils. Follow-up contrast echocardiography was obtained either at the site of angiography or within 24 hours after embolotherapy in all but 1 patient.

All values are reported as mean ± 1 standard deviation. Statistical analysis was performed using Student's *t* test for unpaired data. Differences between the 2 groups were determined to be significant when p values were <0.05.

RESULTS

There were 14 (9 men and 5 women, mean age 37 years, range 23 to 58) of 19 patients with suspected pulmonary A-V malformation who had positive contrast echocardiograms (Figure 1). No complications were observed during or immediately after intravenous injections of the saline solution contrast in any patient. No significant differences in heart rate (R-R interval 804 ± 145 vs 730 ± 156 ms) or relative opacification of the left ventricle (2.9 ± 1.3 vs 2.8 ± 1.2) were noted between patients with A-V malformations and those with atrial right-to-left shunt. There was a significant difference (p <0.001) in number of echocardiographic frames to left atrial appearance of microcavitations after appearance in the right atrium (66 ± 27 frames in patients with A-V malformations vs 21 ± 7 frames in those with right-to-left shunt). In all patients with A-V malformations, left atrial microcavitations appeared at ≥35 frames, whereas in those with right-to-left atrial shunt they appeared within 30 frames of right atrial appearance.

Table I lists the clinical and laboratory findings in the 14 patients with pulmonary A-V malformations. Only 1 patient had auscultatory evidence of an A-V malformation, with a bruit evident in the lower left base. All but 1 patient had telangiectasia and epistaxis. A previous neurologic event was documented in 6 of 14 patients (cerebral abscess in 3, transient ischemic attack in 1, cerebral vascular accident in 1 and an episode of peripheral numbness in 1). Dyspnea was noted in 6 patients (4 only on exertion). The chest roentgenogram was suggestive in 2 patients and diagnostic in 5 with A-V malformations, and 6 of 14 had low partial pressure of oxygen in the arterial blood for their age (6 of 7 had abnormal chest x-rays).

TABLE I Clinical (radiologic and echocardiographic) Findings in Patients with Pulmonary Atrioventricular Malformations Due to Hereditary Hemorrhagic Telangiectasia

Age (yr) & Sex	Te-lang.	RR (ms)	RA–LA Delay	LV Opac	PO_2	CXR	Angio (feed vessel in mm)
49F	+	620	40	2	77	NL	LLL (3)
27M	+	710	43	4	75*	LLL	—
30F	0	630	37	1	88	NL	—
31M	+	730	70	2	91	NL	RUL (3,5); RLL (3)
29M	+	710	50	4	73*	RML ?	LLL (3); RML (6,4)
44F	+	880	38	4	90	LLL	LLL (8)
23M	+	980	65	3	83	NL	LLL (8)
47M	+	930	83	4	58*	LLL	LLL (8,6); RLL (7,6,2)
33F	+	800	77	4	69*	RML	RML (8); LLL (2,5)
32M	+	910	109	1	88	NL	RLL (3)
56M	+	580	62	4	51*	RML ?	RML (12)
33F	+	840	57	3	81	NL	LLL (5); RML (7)
58M	+	1060	127	1	74	NL	—
29M	+	880	75	4	55*	RLL	RLL (6); R hilum (9); L hilum (2)

*Abnormal for patient age.

Angio = pulmonary angiogram; CXR = chest x-ray; L = left; LA = left atrium; LLL = left lower lobe; LV = left ventricle; NL = normal; Opac = opacification; PO_2 = partial pressure of oxygen in arterial blood; R = right; RA = right atrium; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; Telang. = telangiectasia; ? = possible; + = present; 0 = absent; — = not obtained.

Pulmonary angiography was performed in 11 of 14 patients with positive contrast echocardiography, and all had angiographic evidence of A-V malformations. Angiography was not performed in 3 patients (1 refused and 2 had very small right-to-left shunt). A total of 23 malformations were detected in 11 patients; 7 had multiple and 4 had isolated malformations. The majority of A-V malformations (61%) were located in the lower lobes. Patients with 3 to 4+ contrast opacification of the left ventricle (n = 8) had large, isolated or multiple A-V malformations, whereas those with 1 to 2+ opacification (n = 3) had an isolated or small malformation with a feeding vessel <6 mm. Repeat contrast echocardiography immediately after embolotherapy or within 24 hours disclosed a residual right-to-left shunt in all patients; in 2 this shunting was so significant that repeat angiography was performed revealing an additional malformation not apparent during the initial study. These were small, but necessitated embolotherapy. The 1 patient who did not have follow-up contrast echocardiography had a residual large (12 mm feeding vessel) malformation that could not be embolized.

DISCUSSION

Intrapulmonary shunting has been described in patients with presumed congenital pulmonary A-V malformations, and as a consequence of chronic liver disease.[1-3] However, approximately 50% of pulmonary A-V malformations occur in individuals with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome).[3]

Contrast M-Mode echocardiography has been used to diagnosis pulmonary A-V malformation in children and adults.[7-10] However, because 2-dimensional echocardiography provides spatial orientation of the cardiac chambers, we investigated its application in separating patients with intraatrial from those with intrapulmonary shunts. Contrast 2-dimensional echocardiography provided accurate detection of pulmonary A-V malformation. The appearance of microcavitations in the left atrium after initial appearance in the right heart was significantly delayed in patients with A-V malformation compared with that in those with right-to-left shunt at the atrial level.

The clinical sequelae of pulmonary A-V malformation vary, but the majority of patients experience symptoms. White et al[6] have reported epistaxis and dyspnea in 79 and 71%, respectively, of 76 patients with A-V malformations. Neurologic symptoms including transient ischemic attacks, stroke and cerebral abscess were evident in 37, 18 and 9%, respectively of these patients. In our series, isolated or multiple clinical manifestations (epistaxis, neurologic events, dypsnea and abnormal chest x-ray) were evident in all but 1 patient, but chest x-rays were abnormal in only half the group. There were 2 patients without dyspnea, neurologic symptoms or abnormal chest x-rays, and 3 additional patients with only mild exertional dyspnea, but normal blood gases and chest x-rays. Thus, our group of patients illustrates the value of 2-dimensional contrast echocardiography for enhancing diagnostic accuracy.

Pulmonary angiography remains the definitive method to locate pulmonary A-V malformation, and selective embolotherapy has proved to be an effective alternative to surgical resection.[4-6] The goal of embolotherapy is to reduce neurologic complications of A-V malformations and to improve hypoxemia. In our series all but 3 patients underwent angiography, and embolotherapy was performed in 17 of 23 detected A-V malformations resulting in improved arterial oxygenation in all cases. Contrast echocardiography was also used to monitor the effectiveness of embolotherapy. All patients continued to have 2-dimensional evidence of a trivial right-to-left shunt after successful balloon embolization suggesting the presence of A-V malformations too small for angiographic visualization. Importantly, contrast echocardiography was extremely helpful in 2 patients with persistent, significant shunts. Repeat angiography revealed previously occult A-V malformations needing further embolotherapy.

Study limitations: Contrast 2-dimensional echocardiography allows separation of intracardiac from intrapulmonary right-to-left shunt, but definitive conclusions regarding sensitivity in the diagnosis of A-V malformation cannot be made from this investigation, because pulmonary angiograms were not obtained in patients with hereditary hemorrhagic telangiectasia and negative contrast echocardiographic studies. However, it was significantly more sensitive than chest radiography. Although a trend toward greater opacification of the left heart (3 to 4+) was observed in patients with multiple or large, isolated A-V malformations (feeding vessel >5 mm), 2-dimensional echocardiography cannot determine whether multiple A-V malformations are present, nor can it localize the site of the A-V malformation. We carefully reviewed studies to attempt to correlate location of the pulmonary veins with the appearance of microcavitations in the left atrium, but were unable to localize inflow to determine right versus left lung or upper versus lower lobes. Recent investigations have suggested that gradient echo magnetic resonance imaging may be another alternative for the detection of pulmonary A-V malformations.[11] However, the expense of magnetic resonance imaging still makes contrast echocardiography a valuable, readily available noninvasive tool.

Acknowledgment: We express appreciation to Debbie Taylor for preparation of the manuscript.

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Cardiac Myocytes and Dendritic Cells Harbor Human Immunodeficiency Virus in Infected Patients With and Without Cardiac Dysfunction: Detection by Multiplex, Nested, Polymerase Chain Reaction in Individually Microdissected Cells from Right Ventricular Endomyocardial Biopsy Tissue

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Two hundred fifteen patients infected with human immunodeficiency virus (HIV) participated in a prospective longitudinal study of HIV-related heart disease. Evaluation included signal-averaged electrocardiography and echocardiography. Fifteen patients underwent endomyocardial biopsy, 5 had cardiovascular symptoms and 10 did not. Cardiac myocytes or dendritic cells were prepared by individual cell microdissection to sort them from other cell types such as interstitial cells or circulating blood elements. HIV proviral sequences were amplified in samples of 15 to 20 cells of each type by multiplex, nested, polymerase chain reaction and hybridized to ^{32}P-labeled probes specific for regions within the gag and pol genes of HIV-1. The results showed the presence of HIV sequences in myocytes of 2 of 5 patients with cardiac symptoms and in 6 of 10 without. Thus, symptomatic HIV cardiomyopathy did not appear to be a direct consequence of the virus on myocardial cells. In dendritic cells, HIV sequences were detected in 5 of 5 patients with cardiac symptoms and in 8 of 10 with apparently normal ventricular function. Furthermore, dendritic cells were somewhat more numerous in the myocardium of symptomatic than asymptomatic patients. Our studies are the first to directly detect the HIV genome in purified cardiac myocytes from patients with and without cardiac dysfunction. Our findings do not support a direct role of the virus in myocardial dysfunction. However, the results do suggest that the interstitial dendritic cells may be involved in some manner in the development of cardiac dysfunction observed in HIV-infected patients.

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Recent evidence indicates that cardiovascular disease occurs in approximately 6.5 to 6.8% of persons infected with the human immunodeficiency virus (HIV).[1] The types of cardiac involvement in these patients include infectious (bacterial, fungal, protozoal and viral) and neoplastic processes and "intrinsic" cardiomyopathic changes.[1-3] The HIV genome has been detected in deoxyribonucleic acid extracted from autopsy hearts using deoxyribonucleic acid probes.[4] Other investigators report no detection of HIV genome by polymerase chain reaction in autopsy myocardium.[5] New attempts to find HIV in the human myocardium have used in situ hybridization to detect the virus in autopsy tissue.[6,7] The present prospective study was designed (1) to determine whether HIV directly infected the cardiac myocytes and the interstitial dendritic cells in the heart, and (2) to assess the potential role of the virus in the development of myocardial dysfunction and failure observed clinically in some HIV-infected patients.

METHODS

Patient population: From July 1988 to March 1989, 215 HIV(+) patients were screened to participate in a prospective longitudinal study of HIV-associated heart disease. Fifteen were enrolled; 10 patients were free of cardiovascular symptoms and 5 had cardiovascular symptoms (those with cardiovascular symptoms will be

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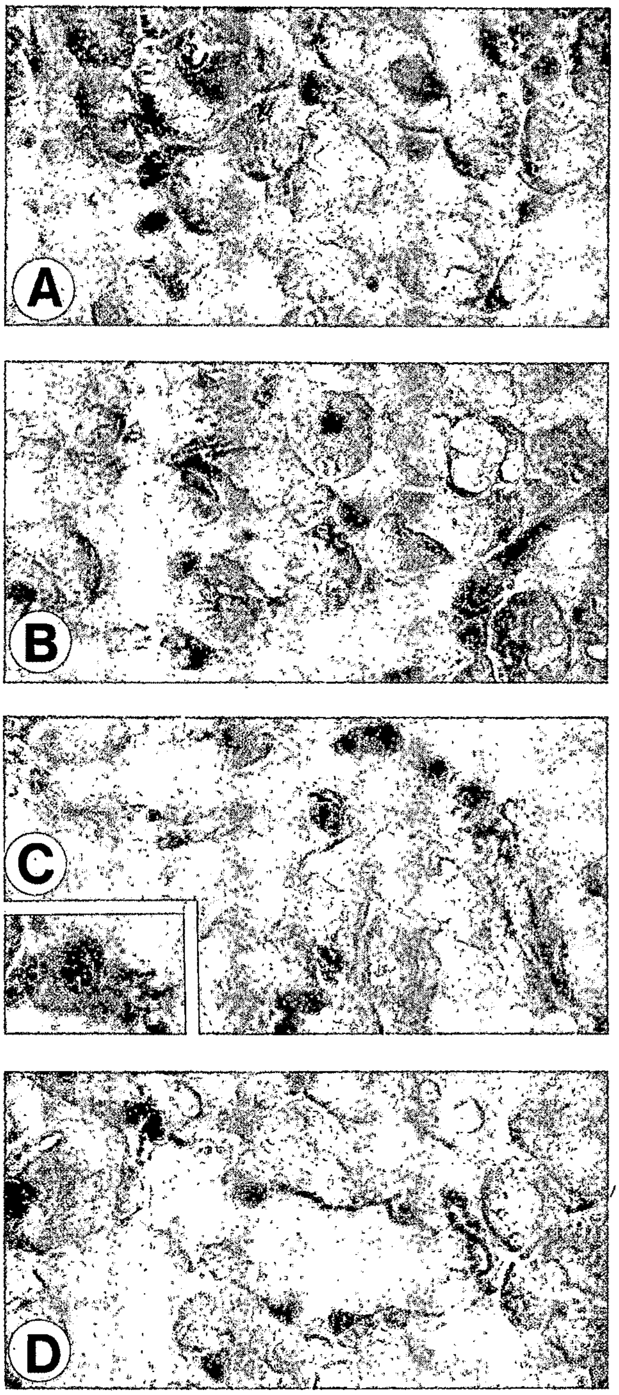

FIGURE 1. Immunoperoxidase stain of dendritic cells using LN3 primary monoclonal antibody in right ventricular endomyocardial biopsy tissue. *A*, cross section of myocardium showing 2 scattered *(brown)* interstitial dendritic cells. *B*, similar section to *A* showing >5 dendritic cells in 1 high-power field. Note the "dendritic" prolongations of the cytoplasm in the cell near the center left of the picture. *C*, dendritic cells in the loose connective tissue surrounding a small capillary in a grazing longitudinal section of the vessel. Inset shows the presence of dendritic cells subjacent to the endothelium. *D*, cross section of a dilated venule (postcapillary or Thebesian) showing MHC-class II antigens. These type of cells were not considered dendritic cells and therefore were not sampled in our study. (*A, B, C*, magnification × 800; *D*, magnification × 600.)

TABLE I Clinical Characteristics of the Study Population

Pt. No.	Age (yr)	CD4 (mm^{-3})	HIV+ (mos)	Race	Clinical Symptoms	Cardiac Symptoms	Pharmacologic Therapy
1	33	220	42	B	LA, PCP	0	0
2	34	926	31	W	LA	0	0
3	22	751	28	W	LA	0	0
4	28	700	26	W	0	0	Acyclovir
5	39	450	18	W	LA	0	0
6	51	494	34	W	LA	0	0
7	35	141	19	W	LA	0	α,β-IFN, A. pent.
8	36	474	6	W	0	0	AZT
9	35	107	45	B	PCP	0	0
10	37	446	20	B	LA	0	0
11S	36	481	12	B	Wt. loss	CHF, VT	Amiodarone, capt., AZT
12S	27	N/A	21	W	PCP	CHF	Digoxin, diuretic
13S	47	600	73	W	LA, ITP	CHF	Enal., AZT, acyclovir
14S	41	8	39	W	LA, lym.	CHF	AZT, diuretic
15S	28	485	48	W	Thrush	CP	AZT, acyclovir, diuretic, aspirin

A. pent. = aerosolized pentamidine; AZT = azidothymidine; B = black; capt. = captopril; CHF = congestive heart failure; CP = chest pain; Enal. = enalapril; HIV+ = human immunodeficiency virus positive; IFN = interferon; ITP = idiopathic thrombocytopenic purpura; LA = lymphadenopathy; lym. = lymphoma; N/A = not available; PCP = *Pneumocystis carinii* pneumonia; VT = ventricular tachycardia; W = white; Wt. = weight.

referred to as "symptomatic" patients to differentiate them from all other patients with other noncardiovascular symptoms) (Table I). The research protocol and informed consent forms were approved by the institutional review board. All patients underwent clinical evaluation including history and physical examination. Laboratory examination included blood chemistry, hemograms, total CD4 counts, microbiologic examination and HIV status determination by enzyme-linked immunosorbent assay and Western blot analysis. The cardiovascular assessment included electrocardiograms with signal averaging,[8,9] echocardiograms, right-sided cardiac catheterization and right ventricular endomyocardial biopsy.

Endomyocardial biopsies: Right-sided endomyocardial biopsy specimens were obtained using a Stanford bioptome. Three to 4 fragments were used for light microscopy, 1 to 2 fragments for ultrastructural examination, and 1 to 2 fragments were frozen for molecular analysis and immunohistochemical studies. The fragments designated for nucleic acid analysis were frozen in dry ice and kept at −80°C.

Autopsy myocardial samples: Myocardial samples were obtained from 4 HIV(−) and 8 HIV(+) hearts during autopsies performed within 6 to 8 hours after death, fixed in ethanol, embedded in paraffin and subjected to the same procedures as previously described, except freezing. Studies of the autopsy specimens (including immunostaining, microdissection, amplification, and so forth) were performed to establish: (1) patterns of immunoperoxidase staining with each of the monoclonal antibodies, and (2) the minimal amount of cells needed to produce consistent results using the polymerase chain reaction amplification of the deoxyribonucleic acid.

Peripheral blood mononuclear cells: Cell samples were available from 8 of the 15 patients who underwent biopsy. The cells had been isolated from residual samples of heparinized blood obtained at the time of the endomyocardial biopsy, and were separated on lymphocyte separation medium (Organon Teknika, West Chester, Pennsylvania).

Cryostat sectioning: Biopsy samples were embedded in OCT compound, frozen and kept at −20°C. Five to 8 μm-thick sections were obtained in a cryostat equipped with disposable blades. New blades and brushes were used every time a new case was cut. The holders (for blade and tissue) were thoroughly washed with a 1:10 dilution of household bleach (Clorox®) for 5 minutes in double-distilled water for 5 minutes and in 100% ethanol for 5 minutes between cases. For each case, 10 sections were obtained and fixed immediately in separate containers with a mixture of acetone-ethanol (1:3), air dried and stored at 4°C until used for immunohistochemical staining. Five thick sections (20 μm) from each biopsy sample were saved in separate polypropylene tubes to be analyzed in parallel with the microdissected cells of the same case.

Immunohistochemistry: The histopathologic and immunohistochemical stains were performed using separate containers and solutions for each slide of each case, thus avoiding potential transfer of deoxyribonucleic acid between the cases during these procedures. Immunoperoxidase staining (Vector) was done with monoclonal antibodies against: (1) leukocyte common

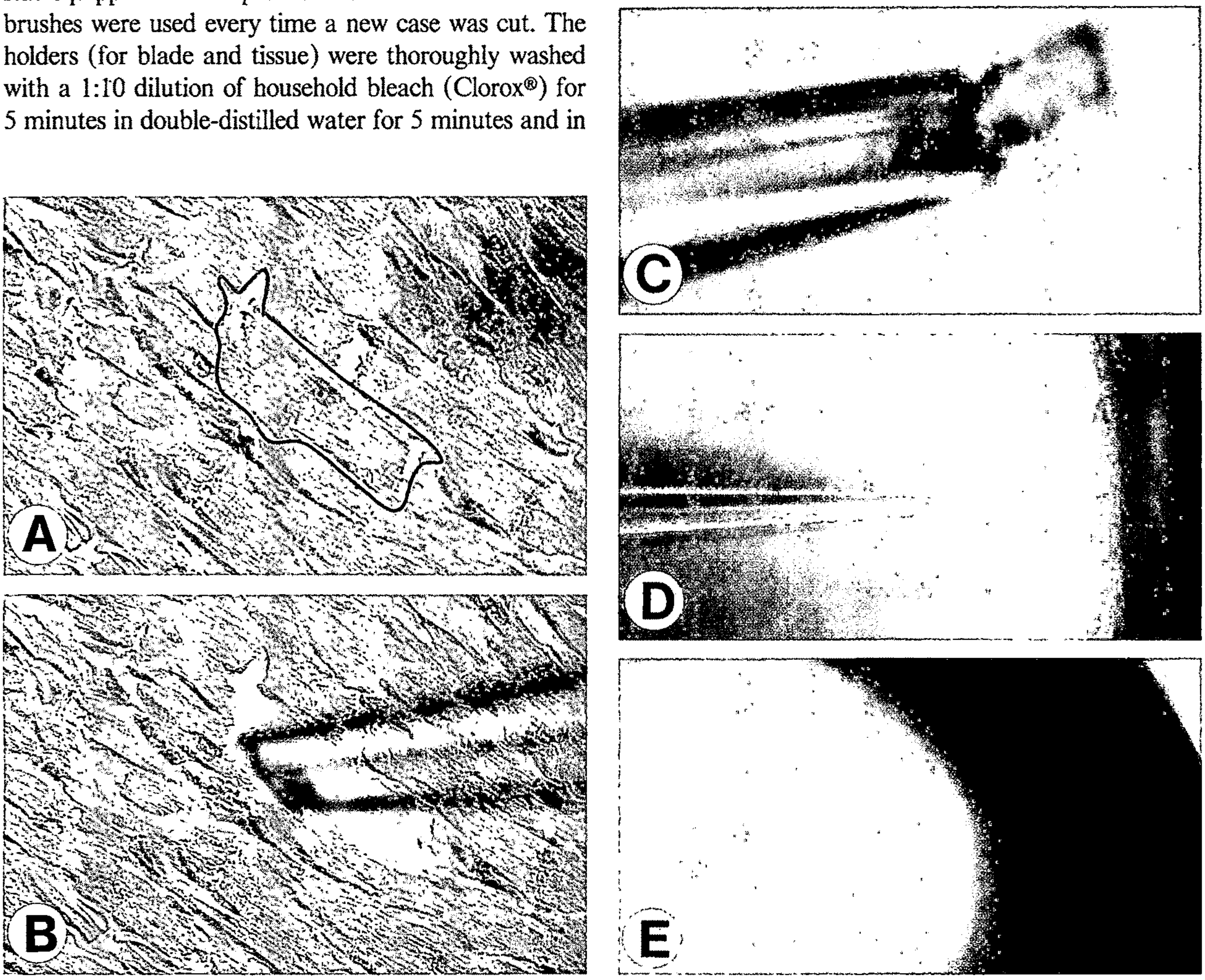

FIGURE 2. Microdissection of immunoperoxidase stained LN3 + interstitial dendritic cells. *A*, longitudinal section of right ventricular endomyocardial biopsy showing 2 pericapillary dendritic cells in the interstitium and a longitudinally oriented myocyte whose contour has been outlined for better definition of its limits. *B*, the myocyte parallel to the 2 dendritic cells in *A* has been carefully removed. Note that neighboring myocytes and interstitial cells are intact in place. A new pipette is being advanced to selectively microdissect another myocyte. *C*, close up of the transferring capillary pipette holding only 1 myocyte. *D*, close up of the deposition of the dissected myocyte at the bottom of a polypropylene 500 μL PCR tube. *E*, confirmation of the presence of 5 to 6 cardiac myocytes at the bottom of the reaction tube. (*A*, *B*, magnification × 800; *C*, magnification × 1200; *D*, magnification × 200; *E*, magnification × 500.)

TABLE II Sequences of Primers and Probes

HIV						Annealing Site of the 5′ End of the Primer.
Gag				GenBank Accession No. K02007		
+SK100	ATCAAGCAGC	CATGCAAAT				1377
R105	CGGCTCTTAG	AGTTTTATAG	AACCGG			1715
+SK38	ATAATCCACC	TATCCCAGTA	GGAGAAAT			1551
+SK39	TTTGGTCCTT	GTCTTATGTC	CAGAATGC			1665
+*SK19	ATCCTGGGAT	TAAATAAAAT	AGTAAGAATG	TATAGCCCTA	C	1595
Pol						
OP3	GGACATAAAG	CTATAGGTAC	AG			2461
++P4	CCTACATACA	AATCATCCAT	GTATTC			3125
R341	CTGTCAACAT	AATTGGAAGA	AA			2501
R343	TAACTTTTGG	GCCATCCATT	CC			2620
*R3422	CACTTTAAAT	TTTCCCATTA	G			2544
Myosin Heavy Chain (Exon 1)					M25133, J04535	
MyHC1	GGAGGCTTTA	CTCTGGGATA	AGGGGG			1321
MyHC2	TATCAGTCAG	TGAGGTACAT	ACCC			1610
MyHC20	CCAGTCACTG	GGCACACATG	TGCA			1417
MyHC40	TCAGACTATG	CAGGCTTGTC	C			1576
*MyHC30	TATGTGCCAC	AGGAGTTCCT	AGGGGAA			1457

*Probe.
+ (13) ++ (14)

antigen for granulocytes and lymphocytes (DAKO); (2) factor VIII for endothelial cells (DAKO); and (3) LN3 for major histocompatibility class II antigens in Langerhans or dendritic cells, or both (Clonab-Biotest, Dreieich, West Germany). All sections were counterstained with hematoxylin.

Microdissection: Myocytes and interstitial and perivascular cells bearing major histocompatibility class II antigen (putatively dendritic cells) were selectively obtained from glass slide-mounted cryostat sections from each of the 15 endomyocardial biopsy specimens (Figure 1). Cells bearing class II antigens located in the intimal (endothelial) surface of venules were not included. Individual cells were microdissected with a set of Narishige hydraulic and mechanical micromanipulators and microinjectors coupled to a Nikon inverted microscope equipped with Hoffman modulation contrast (Figure 2). Emphasis was placed on obtaining a myocyte or dendritic cell or cell fragment containing the nucleus, excluding any adjacent endothelial or smooth muscle cells or remnants of these cells. Myocytes were identified by their sarcomeres, and 15 to 20 were removed individually and transferred to a 0.5 ml polypropylene tube under direct microscopic observation to verify the presence of the microdissected cells inside and at the bottom of the tube (Figure 2). Subsequently, after changing glass micropipets and thoroughly washing the tubing system as described next, 15 to 20 dendritic cells marked by the LN3 antibody were removed and transferred in the same fashion to a separate tube; later, after another wash and micropipet change, periarteriolar dendritic cells were microdissected and kept in separate tubes. Disposable glass micropipettes were manufactured with a Narishige pipet puller and exchanged between cases and also for each type of cell (i.e., myocyte or dendritic cell) microdissected within a case. The pipet holders and Teflon® tubing were thoroughly washed by flushing the system with 50 ml of 1:10 dilution of clorox, followed by flushing with 50 ml of high-pressure liquid chromatography-grade water every time a new type of cell was microdissected and also every time a different case was worked on.

Deoxyribonucleic acid extraction and quantitation: Extraction and quantitation were performed in the usual manner[10] from peripheral blood mononuclear cells, lymph nodes and placenta. Extraction from the thick tissue sections and from the microdissected cells was achieved by adding 75 μL of the polymerase chain reaction buffer to the tubes and subsequently boiling for 15 minutes.

Amplification of proviral deoxyribonucleic acid: All the experiments described next were reproduced 3 times in our laboratory. Extensive precautions to prevent contamination with amplified products were taken. The reagent and sample preparation was performed in separate physical facilities with environmental class II hoods. The ultraviolet light was turned on at all times other than the time of use of the hood by the researcher. Specifically designated sets of instruments including positive displacement Microman pipettors (Rainin, Massachusetts) and pipet tips were use at every step of reagent preparation. Furthermore, the researcher performing these tasks always wore disposable sterile gloves, apron, Tyvek sleeves, surgical hood and mask. The reagents were purchased from different sources as follows: (1) recombinant *Thermus aquaticus* polymerase (Ampli-Taq) from Perkin-Elmer-Cetus; (2) deoxynucleotide triphosphates, calf intestinal alkaline phosphatase and T4 polynucleotide kinase from LKB-Pharmacia; (3) ^{32}P was purchased from New England Nuclear; (4) other chemicals were obtained from Sigma, St. Louis. All solutions were made using high-pressure liquid chromatography grade water.

The polymerase chain reaction in its nested[11] multiplex[12] version was used to amplify a target sequence simultaneously within the gag region (coding for the p24 antigen)[12] of the integrated HIV proviral genome (GenBank Accession no. K02007)[13] and a fragment of exon 1 of the human cardiac myosin heavy chain gene[14] (GenBank Accession nos. M25133 and J04535) in the cells obtained from the endomyocardial biopsy specimens. The fragment of the myosin gene was co-amplified and used as an internal control to demonstrate the presence of human genomic sequences in the reaction tubes, thus indicating the presence of microdissected cells. In addition, another region within the pol gene,[15] HIV-1 genome, was amplified in all the samples after completion of the gag-myosin co-amplification experiments. The amplification buffer composition was: tris-hydroxymethyl-aminomethane hydrochloride 67 mM, magnesium chloride 6.7 mM, ammonium sulfate 16.6 mM, mercaptoethanol 10 mM, ethylene diaminetetraacetic acid 6.7 μM, bovine serum albumin 100 μg/ml, pH 8.8 0.5% Nonident P-40® and 0.5% of Tween 20® (Sigma). The primer concentration for HIV was 25 pM, and for myosin 75 pM. The deoxynucleotide triphosphates were used at 1.5 mM and the

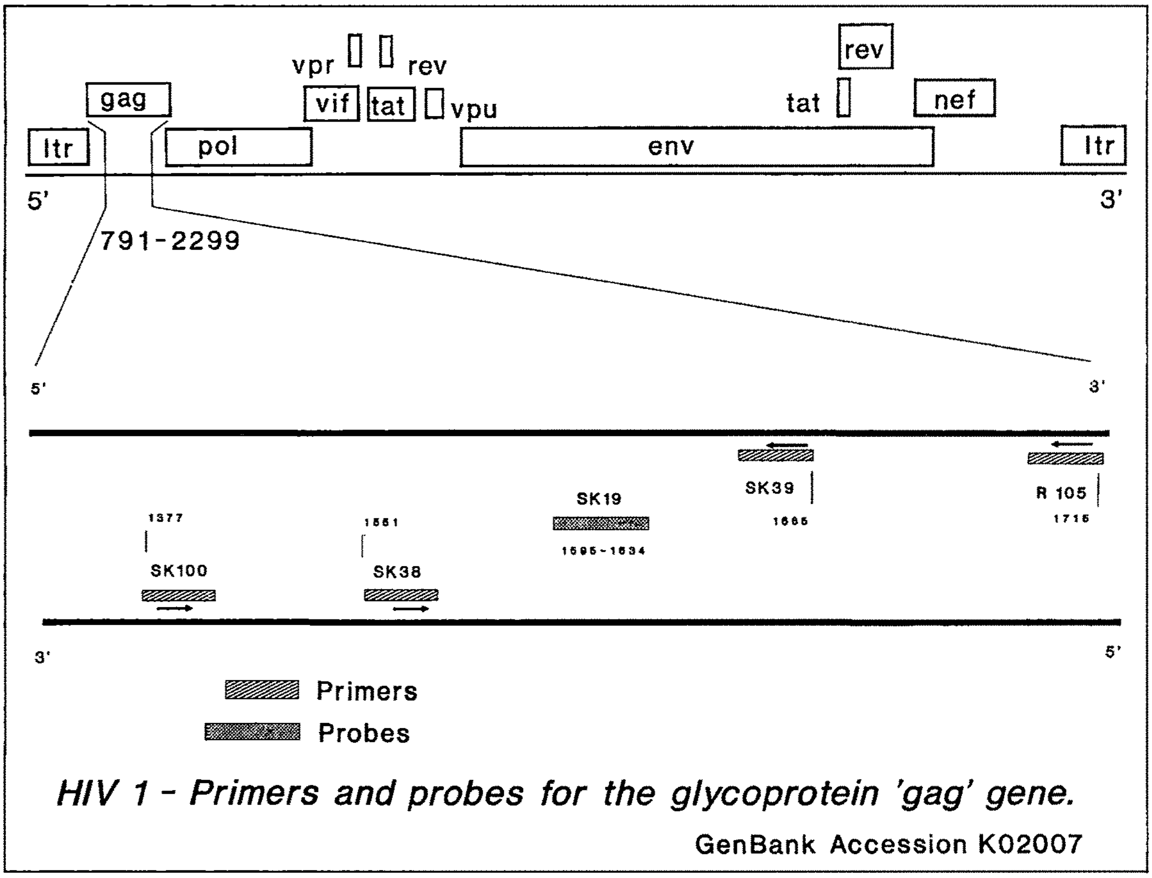

FIGURE 3. Diagrammatic representation of the arrangement of the genes within the 9,737 base long sequence of the San Francisco isolate of human immunodeficiency virus (HIV-1) (Genbank Accession no. K02007). The lower part of the figure represents the area within the "gag" gene used as the target of amplification through the nested procedure. Primers SK100 and R 105 flank the 339 base pair amplified fragment produced by the first (outer) nest of amplification. The 4 digit numbers represent the exact position of the 5' end of each primer. An aliquot of the PCR mixture containing this 339 base pair amplified product becomes, in turn, the target flanked by primers SK 38 and SK 39, thus amplifying a 115 base pair product, which is in turn hybridized to the ^{32}P-labeled probe SK 19 probe. The same strategy was used to co-amplify exon 1 of the cardiac myosin heavy chain in the microdissected cells and the "pol" gene of HIV.

AmpliTaq at 3 U per sample tube. The sequences of primers and probes used in these experiments are listed in Table II. The primers and probes were synthesized in a Milligen-Biosearch Cyclone oligo-nucleotide synthesizer (Bedford, Massachusetts). The sequences were examined for homology with other human, viral or bacterial sequences in Release 65 of the GenBank computerized database (IntelliGenetics, Inc., Mountain View, California) using the Pustell sequence analysis program version 2.02. (International Biotechnologies, New Haven Connecticut) to avoid primer dimer or concatemer artifacts.

Nested polymerase chain reaction was used to enhance the strength of the HIV and myosin signals obtained from the low numbers of cells. This approach uses 1 primer pair (outer nest) to amplify a target sequence of the desired gene present in minute amounts (Table II and Figure 3). Once amplified, 5 μL of the first product were transferred to a new tube containing a second primer pair internal to the first or outer primer pair and amplified again, thus yielding a very strong signal. The efficiency of amplification of the inner nest is increased because the number of "target" molecules at the beginning of the reaction is more numerous and shorter in length (only a few hundred bases long), thus allowing for more efficient denaturation and accessibility of the primers to their target sites of complementarity for annealing and subsequent extension. For added specificity a ^{32}P-labeled probe internal to the inner nest was used to detect the HIV (gag and pol) and the myosin target sequences.

The amplification was performed in a thermal cycler (Perkin-Elmer). The deoxyribonucleic acid content of all the control samples and the peripheral blood mononuclear cells was standardized to use 0.1 μg per tube. To ensure our ability to detect product from the small number of cells microdissected, experiments were performed to amplify serial 10-fold dilutions of pooled deoxyribonucleic acid extracted from lymph node biopsy specimens from HIV(+) patients with acquired immune deficiency syndrome. Positive signals for co-amplification of myosin and gag of HIV were obtained from as little as 10 pg of deoxyribonucleic acid inoculum amplified through the nested procedure. The controls consisted of reaction buffer plus: (1) primers, without any other deoxyribonucleic acid inoculum; (2) human HIV(−) genomic deoxyribonucleic acid; (3) deoxyribonucleic acid from human ventricular myocardium obtained at autopsy from HIV(−) patients; (4) deoxyribonucleic acid from human ventricular myocardium of HIV(+) patients obtained at autopsy; and (5) pooled lymph node deoxyribonucleic acid from 5 different HIV(+) patients. The amplification cycle for the outer nest was repeated 50 times for microdissected cells and 30 times for the control and peripheral blood mononuclear cells as follows: 1-minute, 15-second denaturation at 95°C; 2-minute annealing at 52°C, and extension of 3 minutes at 72°C. The amplification cycle for the inner nest was repeated 50 times for microdissected cells and 20 times for the control and peripheral blood mononuclear cells. The parameters were the same except for an extension of 2 minutes at 72°C.

Southern hybridization: The amplified deoxyribonucleic acid product underwent electrophoresis in 3% Nu-Sieve and 0.8% SeaKem agarose gels (FMC, Rockland, Maine) at 100 V for 4 hours. The gels were stained in a 1 μg/ml ethidium bromide solution and photographed under ultraviolet light, and then denatured in sodium hydroxide 0.4 N, sodium chloride 0.5 M for 30 minutes. Subsequently the deoxyribonucleic acid was transferred to a nylon membrane (Oncor, Gaithersburg) using the Southern method.[10] The acid product was then baked in a vacuum oven at 80°C for 1 hour before hybridization, and then hybridized with 10 μg of ^{32}P-end-labeled probe for 48 hours using 10 μg/50 ml of ^{32}P end-labeled probe according to conventional methods.[10] Autoradiograms were obtained at 48 to 72 hours.

RESULTS

Patients: The patient population comprised a total of 15 persons (Table I). Their ages ranged from 28 to 52 years (mean 38.6). Eleven patients were black and 4 were white. Ten had acquired immune deficiency syndrome and 5 did not. The patients were homosexual, bisexual or transsexual. One patient was also an intravenous drug abuser. Six patients were receiving azidothymidine prophylactic therapy; in 6 other patients it had been discontinued and 3 patients never received the drug. Five patients had evidence of cardiovascular disease at the time of enrollment. The clinical cardiovascular findings consisted of right ventricular failure, pericardial effusion, diffuse T-wave inversion, right bundle branch block or delayed potentials on the signal-averaged electrocardiogram. The echocardiogram showed global hypokinesia and left ventricular diastolic pressure increased in 4 patients. Right atrium and ventricle were markedly dilated in the fifth patient. One had concomitant pericardial effusion.

Light microscopic examination of all biopsy specimens was normal, without evidence of myocarditis. Ultrastructurally, 2 subjects had interferon-associated inclusions in the endothelial cells and 1 also showed these inclusions in macrophages. Both of these patients had cardiovascular symptoms. Viral particles or their precursors were never seen either in myocytes or in other cells present in the heart biopsy tissue. Immunohistochemical analysis also failed to demonstrate inflammatory cells. The use of the LN3 antibody directed to class II molecules revealed that interstitial cells bearing

TABLE III Dendritic Cell Score and Southern Blot Hybridization Results

	Score DC	TIS MyHC	TIS GAG	TIS POL	MYO MyHC	MYO GAG	MYO POL	DC MyHC	DC GAG	DC POL	DC+A MyHC	DC+A GAG	DC+A POL	PBMC MyHC	PBMC GAG	PBMC POL
1	0.5	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+
2	2	+	+	+	+	0	+	+	0	0	+	+	+	+	+	+
3	1	+	+	0	+	+	0	+	0	0	+	+	0	–	–	–
4	3	+	+	+	+	0	0	+	+	+	+	+	+	+	+	+
5	0.5	+	+	0	+	+	0	+	+	0	–	–	–	–	–	–
6	2	+	+	+	+	+	0	+	+	0	+	+	+	+	+	+
7	2	+	+	+	+	0	0	+	+	0	–	–	–	–	–	–
8	3	+	+	+	+	0	0	+	+	+	–	–	–	+	+	+
9	0.5	+	+	+	+	0	0	+	+	+	–	–	–	–	–	–
10	2	+	+	+	+	+	0	+	+	+	+	0	0	–	–	–
11S	1	+	+	+	+	0	0	+	+	+	–	–	–	+	+	+
12S	3	+	+	+	+	0	+	+	+	+	–	–	–	–	–	–
13S	4	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+
14S	1	+	+	+	+	0	0	+	+	+	–	–	–	+	+	+
15S	2	+	+	+	+	0	0	+	+	0	–	–	–	–	–	–
Total	27.5	15	15	13	15	6	4	15	13	8	6	5	4	8	8	8
Average	1.7															

DC = dendritic cells; DC+A = periarteriolar dendritic cells; MyHC = myosin heavy chain; MYO = myocytes; PBMC = peripheral blood mononuclear cells; S = symptomatic; TIS = 20 μm thick whole tissue sections; + = positive; 0 = negative; – = not available.

these antigens were present in the myocardium of HIV-infected patients. These cells were present around capillaries and larger vessels including arterioles and venules, being more conspicuous around the venules. These cells were also present in autopsy hearts with the same pattern. The LN3 antibody also stained class II molecules on the surface and cytoplasm of the venular endothelial cells. However, these latter cells were clearly distinguishable from interstitial dendritic cells by their location on the luminal surface of the venules and by the presence of reactivity for factor VIII-associated antigen as demonstrated by immunohistochemical staining in adjacent sections.

Detection of human immunodeficiency virus 1 gag and pol gene sequences in myocardial cells from autopsy tissue, peripheral blood mononuclear cells and endomyocardial biopsy tissue: Initial studies were performed on autopsy material to establish (1) the minimal number of cells needed to obtain amplification, and (2) the parameters to be used in such amplification. The results of the polymerase chain reaction were considered positive for the presence of HIV only if the following 3 criteria were met: (1) Reagent controls that contained no deoxyribonucleic acid template were negative for both myosin and HIV target sequences (Figure 4, column 1). (2) Control samples containing deoxyribonucleic acid known to be negative for HIV showed amplification of the cardiac myosin sequence but no evidence of HIV product formation (Figure 4, column 2). (3) The HIV(+) control samples showed co-amplification of the myosin sequence as well of amplification of the HIV target sequence (Figure 4, column 4).

All samples of autopsy heart tissue from HIV(−) patients (n = 14) were positive for myosin and negative for HIV (Table III). All autopsy samples from HIV(+) (n = 11) were positive for myosin and HIV (data not shown). All the samples of peripheral blood mononuclear cells from 8 of the patients enrolled in the protocol were positive for amplification of the myosin, gag and pol genes. All the thick biopsy tissue sections were positive for myosin. Likewise, HIV and gag sequences were detected in all thick section samples (Table III, Figure 4) and HIV pol sequences were present in 13 of 15 patients (Table III; Southern hybridization for pol not shown). Cells microdissected from endomyocardial biopsy tissue showed the presence of the marker myosin gene in every 1 of the samples (myocytes and dendritic cells). This demonstrated that the polymerase chain reaction as performed in these studies was sufficiently sensitive to detect target sequences in as few as 15 to 20 cells. The positive signal for myosin also showed that the treatments associated with the immunoperoxidase-staining procedure (peroxidase treatment, and so forth) did not degrade the deoxyribonucleic acid to a point that it was no longer useful for polymerase chain reaction.

The presence of HIV-1 proviral genomic sequences within the myocytes did not discriminate between symptomatic and asymptomatic patients. Six of 10 (5 of 10 for gag and 2 of 10 for pol) asymptomatic patients had HIV present in myocardial cells (Table III), whereas only 2 of 5 symptomatic patients (1 of 5 for gag and 2 of 5 for pol) had HIV sequences in myocytes (Table III).

In addition to myocytes, we examined purified interstitial dendritic cells for the presence of HIV. Before microdissecting the dendritic cells, we quantitated them according to the following scoring system: The number of cells per 5 high-power fields was counted and then translated into a predefined score as follows: score of 1 = 1 to 5 cells; 2 = 5 to 10 cells; 3 = 15 to 20 cells; and 4 = >25 cells (Figure 1). The average score of interstitial dendritic cells for the group of 15 patients was 1.7 (Table III). However, in the asymptomatic patients it was 1.65 compared with 2.2 in the symptomatic patients. Analysis of the amplification results in the asymptomatic patients showed that the dendritic cells were positive by for gag in 8 of 10 and for pol in only 5 of 10 patients (Figure 4). Among the symptomatic patients the dendritic cells showed HIV gag sequences in 5 of 5, and pol sequences in 3 of 5 patients (Table III).

DISCUSSION

Demonstration of HIV in the cardiac myocytes of HIV-infected patients has been elusive. Recent studies of HIV-related heart disease by in situ hybridization showed sparse signals, involving only 1 or a few cells per section; precise identification of the nature of the target cells was sometimes difficult, with the possible source of the signals being lymphocytes, macrophages[6] or even endothelial cells.[7]

In the present study, the presence or absence of cardiac dysfunction in 5 symptomatic and 10 asymptomatic HIV-infected patients did not correlate with CD4 counts, azidothymidine therapy, or full-blown acquired immune deficiency syndrome. Moreover, none of these patients showed any evidence of myocarditis as defined in the Dallas criteria.[16]

We investigated the presence of HIV within myocytes or cardiac interstitial cells by means of the polymerase chain reaction. A potential drawback of this technique is that the amplified target sequence can contaminate laboratory facilities, instruments, reagents, and so on, leading to production of false-positive results.[12] We took extensive precautions to avoid contamination and found no contamination of our reagents. Co-amplification of HIV and myosin genes proved that there were no inhibitors of the reaction and verified that deoxyribonucleic acid from the microdissected cells was present in the individual sample. The use of a ^{32}P-labeled probe internal to primer sites further increased specificity in identifying the target sequence. We did not attempt to quantify the proviral load. This could be particularly misleading because myocytes can be binucleate, tetraploid or even polyploid in different circumstances of cardiac overload, thus rendering normalization to copy number per cell quite ambiguous. Furthermore, differences in the kinetics of co-amplification for the different combinations of primers used in our experiments preclude arriving at quantitative results.

The finding that the thick biopsy tissue sections were all positive for myosin and at least 1 of the HIV genes examined demonstrated that the provirus was definitely present in the heart biopsy specimen of every patient studied (Table III). The use of 2 separate target regions of HIV for amplification provided us with certainty of the detection of HIV, and avoided possible false-negative results due to mutations in the HIV genome (which occur at high rate). The absence of a signal for "pol" in cases 3 and 5 (Table III) in the whole tissue and in the microdissected cells was interpreted to be the result of a mutation in the target region of the

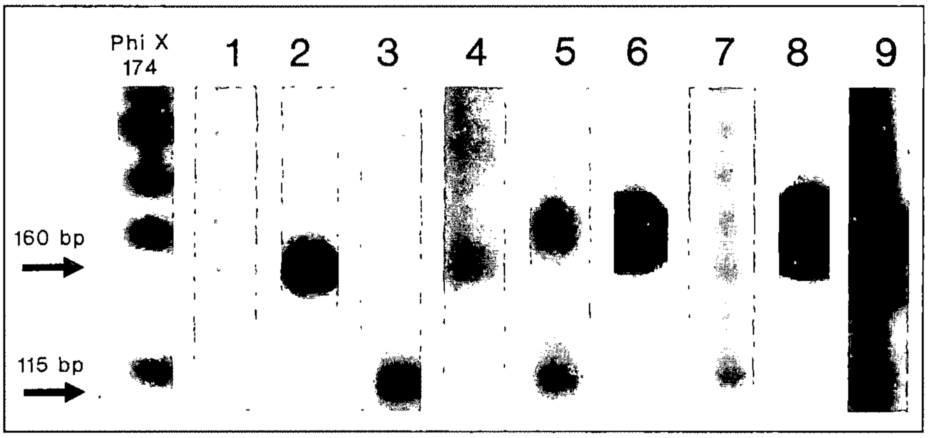

FIGURE 4. Representative findings of multiplex PCR to detect myosin heavy chain gene and human immunodeficiency virus (HIV)+ in endomyocardial biopsy specimens. Control samples: 1 = buffer control with no signals for myosin heavy chain or HIV; 2 = HIV negative control showing a positive signal for myosin heavy chain (160 bp); 3 = HIV + sample amplified with HIV (gag) primers only showing a positive signal for HIV; 4 = deoxyribonucleic acid pooled from lymph nodes from HIV + patients (10 pg inoculated in the PCR tube) showing signals both for myosin heavy chain and HIV; 5 = thick (20 μm) section of a biopsy tissue sample from a patient with cardiac symptoms showing both signals. Microdissected cells: 6 = myocytes showing a signal positive for myosin heavy chain only; 7 = myocytes showing myosin heavy chain and HIV signals; 8 = dendritic cell showing a positive signal for myosin heavy chain only; 9 = dendritic cells showing signals for myosin heavy chain and HIV; Size marker (restriction fragments of phage X 174 digested with HaeIII restriction endonuclease). bp = base pair length of the amplified fragment.

pol gene. No attempt was made in our experiments to design new primers to overcome this problem.

The use of microdissection provided the accuracy and the selectivity necessary to study cardiac myocytes and interstitial dendritic cells. The transfer of a cytoplasmic or nuclear component from cells other than myocytes into the myocytes during the process of sectioning is a very remote possibility that we considered in our experimental design, as described in the methods. The only situation in which deoxyribonucleic acid transfer may theoretically occur is during the actual slicing of the frozen section by the new microtome blade. This possibility is minimized by the fact that the tissue is frozen solid at −20°C and the microtome blade is at the same temperature, therefore avoiding any "micro-melting" of cellular components into the blade and the subsequent transfer. Besides, the cytoplasmic and nuclear matrices of the cells are bound in the frozen state and structural proteins, nuclear proteins are in fact sectioned through and not smeared. Thus, in the experimental design of our study, we had to assume that there was no carryover of deoxyribonucleic acid from cell to cell in the process of cutting frozen sections. Furthermore, the consistency of the positive or negative results of amplification for the negative (reaction mixture) and positive controls, and each case and cell type during the repetition of the experiments in the tissue sections and in the microdissected cells, lowers the likelihood of random, artifactual amplification signals being produced.

Thus, our studies demonstrate that (1) cardiac myocytes can be and are infected by HIV in patients, (2) the frequency of detection of infected myocytes is similar for both symptomatic and asymptomatic patients, (3) a direct lethal effect by the infecting virus on the myocytes is unlikely to be the cause of HIV associated myocardial failure, (4) dendritic cells are increased in number in the heat of HIV-infected patients, and (5) dendritic cells harbor HIV more often than the myocytes.

The mechanism by which HIV infects the cardiac myocytes remains elusive. Evidence shows that HIV can enter rhabdomyosarcoma[17] and other cells that do not bear CD4 molecules.[18] In humans, dendritic cells[19,20] are present in the heart, and become prominent in transplanted hearts[21] and in myocarditis.[22] The theoretical mechanism by which these cells may play a role in cardiac dysfunction may involve cytokines such as tumor necrosis factor.[23-26] In animals, this cytokine inhibits myocyte contractility in response to β-adrenergic stimulation[27] by altering G protein function,[27,28] and in turn interfering with signal transduction across the sarcolemma. In clinical settings, tumor necrosis factor may be a an important mediator of heart failure in septic shock[29] and possibly "cardiomyopathy."[30] Further research in these aspects may elucidate the exact mechanisms that mediate myocardial contractility dysfunction in HIV infection.

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Moricizine (Ethmozine HCl) — A New Antiarrhythmic Drug: Is It Unique?

Philip J. Podrid, MD

The latest antiarrhythmic agent to be approved is moricizine (ethmozine hydrochloride), which is in some ways a unique agent. It was first synthesized in the U.S.S.R. and was used there for many years before its introduction to the U.S. where it has been investigated since 1977. It is a phenothiazine derivative, but is devoid of many of the adverse effects ascribed to this class of drugs. Whereas most of the available data involve its use for ventricular arrhythmia, the drug has electrophysiologic properties suggesting a role in supraventricular arrhythmias, although data are as yet limited.

Electrophysiologic effects: Moricizine is a class 1 antiarrhythmic agent, its major effect being a concentration-related blockade of the sodium channel and inhibition of sodium ion currents[1] (Table I). The reduction in the maximal upstroke velocity (Vmax) of phase 0 of the action potential results in a reduction in the velocity of impulse conduction throughout tissue that generates a fast sodium-initiated action potential, i.e., atrial and ventricular myocardium and the His-Purkinje system. Similar to other antiarrhythmic drugs, moricizine demonstrates the property of use dependency (i.e., its electrophysiologic actions are more pronounced at higher frequencies of stimulation).[2] These electrophysiologic effects resemble those produced by class 1C antiarrhythmic agents. However, similar to the class 1B agents, the drug increases the rate of membrane repolarization, shortening the action potential duration as a result of a shortening of phases 2 and 3.[1]

Moricizine alters the membrane threshold potential, making it less negative, thereby increasing the amplitude of current necessary to depolarize the cell and reducing membrane excitability.[3] As a result of the shortening of phases 2 and 3, moricizine depresses early delayed afterpotentials, a form of trigger automaticity.[1] Although moricizine does not alter the slope or rate of phase 4 depolarization, it does reduce the spontaneous automaticity of Purkinje fibers, especially during ischemia or in the presence of hypokalemia, as a result of the shift in threshold potential to a less negative level, increasing the duration of time before threshold is reached and an action potential generated.[4] Late or delayed afterpotentials, another form of triggered activity which results from catecholamines, ischemia or an acute myocardial infarction or with digitalis toxicity, are depressed by moricizine.[5]

These electrophysiologic data suggest that moricizine may be effective against arrhythmias regardless of their mechanism, i.e., reentry, enhanced automaticity, or triggered automaticity due to early or late delayed afterpotentials. Studies in the intact animal have confirmed that moricizine is effective against ventricular arrhythmias resulting from a myocardial infarction, epinephrine and aconitine, but it is not effective against strophanthidin.[1] Whereas the electrophysiologic effects of moricizine have been evaluated primarily in ventricular tissue, the drug also has antiarrhythmic actions on atrial tissue that resemble those in the ventricular myocardium.[1] However, this has not been sufficiently studied.

In the clinical electrophysiology laboratory, oral moricizine significantly shortens the sinus cycle length, but has no significant effect on sinus node recovery time or sinoatrial conduction time.[6] The drug does not effect the refractory periods of the atrial and ventricular myocardium, His-Purkinje system or atrioventricular node, and there is no change in the atrial cycle length at which nodal Wenckebach develops; however, it does slow the velocity of impulse conduction through these structures. As a result, the AH and HV intervals are significantly prolonged.[6]

On the surface electrocardiogram, the PR and QRS intervals are prolonged, reflecting the drug's membrane electrophysiologic effects. The JT interval, or repolarization time, is not altered or may be insignificantly shortened.

Pharmacology: Moricizine is available for oral use and the recommended doses are 200 to 400 mg administered orally 3 times daily based on dose-ranging studies[7] (Table II). The peak plasma level of the drug is achieved 1½ hours after oral administration. Although rapidly and completely absorbed, the systemic bioavailability of moricizine is only 38%, a result of its substantial and rapid first-past clearance by the liver.[8] The clearance of the drug follows 2 compartment pharmacokinetics. There is a rapid distribution phase, with a

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TABLE I Electrophysiologic Effects of Moricizine

Cellular
Sodium channel blockade—rate of depolarization and impulse conduction velocity decreased (class 1C activity)
Rate of repolarization, increased action potential duration shortened (class 1B activity)
Membrane threshold potential less negative—reduced membrane excitability and automaticity
Early and late afterpotentials depressed
Clinical
Shortens sinus cycle length
Prolongs AH interval—PR prolongation
Prolongs HV interval—QRS widening
No change in refractory periods of atrium, ventricle, AV node or His Purkinje system
Slows anterograde and retrograde conduction of accessory pathway

AV = atrioventricular.

drug half-life of 4 to 20 minutes, whereas the half-life resulting from the terminal elimination phase is longer, usually 2 to 6 hours but as long as 13 hours in patients with significant heart disease. About 95% of the drug is bound to plasma proteins, involving both albumin and α-1-acid glycoprotein. The volume of distribution of moricizine is 300 liters, suggesting that there is extensive peripheral tissue binding.

Hepatic metabolism of moricizine is almost complete and many metabolites have been identified. Most appear to be devoid of antiarrhythmic activity, although 2, moricizine sulfoxide and phenothiazine-2-carbon acid ethyl ester sulfoxide, have some antiarrhythmic activity, but this is well established. The presence of congestive heart failure does not appear to alter the pharmacokinetic properties of moricizine, but associated hepatic dysfunction may affect drug metabolism and its half-life.

Drug interaction: Only a few interactions have been reported. There are no changes in the kinetics of warfarin or the prothrombin time when moricizine is administered.[9] Cimetidine, which inhibits hepatic oxidative enzymes, reduces the clearance of moricizine by up to 48%,[10] but this is not clinically significant. There are no significant interactions with digoxin or propranolol.

An interesting interaction with theophylline has been observed. As a result of a moricizine-induced increase in hepatic metabolism, the rate of theophylline clearance is increased and its half-life shortened. This may have clinically important effects in patients with asthma.

Hemodynamic effects: In the *in vivo* dog heart, moricizine has no effect on heart rate or blood pressure; vasomotor responses to norepinephrine, acetylcholine, histamine and angiotensin are not altered by the drug. Myocardial contractility of the dog heart and left ventricular hemodynamic parameters are not altered.

TABLE II Pharmacology of Moricizine

Dose	200–400 mg 3 times daily (oral)
Absorption	Rapid and complete
Peak levels	1½ hours
Bioavailability	38%
Elimination half-life	2–60 hours (normal subjects) 6–13 hours (heart disease)
Protein binding	95%
Metabolism	Hepatic (first-pass effect) Multiple metabolites (? activity)
Drug interactions	Cimetidine Theophylline

? = unknown.

The clinical experience with moricizine in humans confirms its lack of significant effects on left ventricular contractility. There is no change in global right or left ejection fractions during therapy when evaluated with 2-dimensional echocardiography or radionuclide ventriculography, even in the subset of patients with a reduced left ventricular ejection fraction.[11] When exercise testing is used as a measure of left ventricular function, moricizine produces no change in exercise duration, resting or peak heart rate or resting and peak blood pressure.[11] With use of invasive hemodynamic measurements in patients at rest as well as during supine bicycle exercise, the drug does not alter mean pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac index, stroke volume index, left ventricular stroke work index or systemic vascular resistance.

Clinical trials: Moricizine has been well studied in patients with a wide range of ventricular arrhythmia. Initial clinical trials involved patients with little or no heart disease who had frequent ventricular premature complexes (VPCs) and moricizine was reported to be very effective, significantly reducing VPC frequency, including repetitive forms, i.e., couplets and runs of nonsustained ventricular tachycardia (VT).[12,13]

In a trial of 88 patients, moricizine therapy was administered for >1 year.[14] There was a >70% reduction of VPCs in 60% of patients during the entire follow-up period. In the Cardiac Arrhythmia Pilot Study (CAPS) involving 98 patients with a recent myocardial infarction, 66% of patients responded to doses of 600 to 750 mg/day.[15] After a 1-year follow-up, 65 patients continued to take moricizine with continued arrhythmia suppression. Moricizine is currently the only agent being used in the Cardiac Arrhythmia Suppression Trial (CAST)-II as the other agents, encainide and flecainide, were withdrawn because their use resulted in increased sudden death.[16] Unfortunately, long-term data regarding efficacy and outcome with moricizine are not yet available.[17]

In a number of trials involving patients with frequent VPCs, moricizine has been compared with other antiarrhythmic drugs. In a double-blind, placebo-controlled comparative trial involving moricizine and propranolol, 20 patients were initially randomized to 1 week of therapy with moricizine (600 to 900 mg/day), moricizine plus propranolol, or propranolol alone (120 mg/day). Efficacy, defined as a >75% reduction in arrhythmia, was achieved in 70% of patients in whom VPCs were reduced 86% during ethmozine therapy. Only 10% of patients responded to propranolol and the reduction in VPCs was 41% ($p < 0.05$). Of the 14 patients who had runs of nonsustained VT, 79% had abolition of these forms during moricizine therapy while taking propranolol (response rate was 50%) ($p =$ not significant). In a comparative trial, 29 patients, in random fashion, received 10 days of therapy with moricizine and disopyramide. With moricizine therapy, 52% of patients responded and there was a 90% reduction in VPCs compared with a 31% response rate and 65% reduction in VPCs ($p < 0.05$) with disopyramide. There was no significant difference in the reduction of couplets or runs of nonsustained VT.

In a third study involving 21 patients, moricizine (600 to 1,200 mg/day), quinidine (1,200 to 1,600 mg/day) or placebo were administered for 2 weeks. The response rate to the 2 agents (67% moricizine and 71% quinidine) was similar as was the mean reduction in VPCs (95%) and nonsustained VT (90%). The CAPS provided data permitting a comparison of moricizine (600 to 900 mg/day) with encainide (105 to 180 mg/day) and flecainide (200 to 400 mg/day).[15] The response rate to these 3 agents was 66, 79 and 83%, respectively.

Moricizine has also been evaluated in patients with a history of a serious sustained ventricular tachyarrhythmia. In a group of 82 patients with a history of ventricular fibrillation, sustained VT or symptomatic nonsustained VT, who had a high density or spontaneous ventricular arrhythmia, the antiarrhythmic effect of moricizine was evaluated with ambulatory monitoring and exercise testing.[18] Criteria for efficacy were total elimination of runs of nonsustained VT, >90% reduction in couplets and >50% decrease in VPC frequency using both methods of evaluation. Overall, 40% of patients responded to the drug. Response rate was related to the nature of the presenting arrhythmia and was 62% in those with nonsustained VT, 33% in patients with ventricular fibrillation and 19% in patients with sustained VT. Additionally, the drug was more effective and the response rate higher among patients with better left ventricular function. When left ventricular ejection fraction was >40%, 35% of patients responded compared with an 18% response rate among patients with an ejection fraction <40%. From the U.S. data base involving 263 patients with a serious ventricular arrhythmia refractory to previous antiarrhythmic drugs, 48% were judged to have responded to the drug; as previously noted, the response rate was greater in patients with nonsustained VT (61%) than in those with a sustained tachyarrhythmia (42%).[19]

Similar to other drugs, moricizine is less effective when evaluated by electrophysiologic techniques. An early study involving 47 patients reported that suppression of VT induction was achieved during moricizine therapy in 18% of patients, whereas those with nonsustained VT induced at baseline had a noninducibility rate of 27%.[6] In a review of the U.S. data base, there were 117 patients with paired electrophysiologic studies.[19] Among those with sustained VT induced in the baseline study, the drug prevented reinduction in 25%, whereas noninducibility was achieved in 36% who had nonsustained VT at baseline. Overall, noninducibility was achieved in 29%. However, an additional 45 patients with baseline electrophysiologic tests did not undergo a repeat study during moricizine therapy because of drug discontinuation for side effects or drug inefficacy based on noninvasive evaluation. When these patients are included in the analysis, the overall efficacy rate is 21%. In other studies, noninducibility with moricizine with electrophysiologic techniques is as low as 5%.[18]

Unfortunately, data on the outcome of long-term therapy with moricizine in patients with serious ventricular arrhythmia are sparse. When noninvasive methods were used to judge efficacy, the sudden death rate was 12%, whereas a nonfatal recurrence occurred in 12% after a 13-month follow-up.[18] Of 28 patients responding to moricizine (based on electrophysiologic testing) and continuing to take it for a mean of 6.8 months, there were 3 sudden deaths (10.7%) and a nonfatal recurrence in 6 (21.4%).[19]

Although moricizine has effects on atrial myocardium and the atrioventricular node, data on the role of this agent for therapy of supraventricular arrhythmias are sparse and no controlled studies are available. In 1 small series of 4 young patients with an ectopic atrial tachycardia, moricizine was effective in each patient.[20] An intravenous preparation of moricizine was evaluated in the U.S.S.R. in patients with supraventricular tachycardia. Among 16 patients with an accessory pathway, the drug (1.5 to 2 mg/kg) terminated the induced tachycardia in 9 patients, and prevented its reinitiation in 8.[21] In the remaining patients, the cycle length of the induced supraventricular tachycardia was lengthened. In many patients the drug did slow or abolish anterograde and retrograde conduction over the accessory pathway and prolonged its refractory period. In a second study, intravenous moricizine (1.5 to 2 mg/kg) was administered to 11 patients with atrioventricular nodal

TABLE III Most Frequent Adverse Effects from Moricizine—U.S. Data Base (n = 1,256)

	Adverse Reaction (%)	Drug Discontinued (%)
Overall	71.5	9
Cardiac	16.8	2.6
Arrhythmia aggravation	8.0	?
Congestive heart failure	7.1	0.9
Chest pain	2.8	?
Nervous system	37.7	0.6
Dizziness	15.1	
Headache	8.0	
Nervousness	2.5	
Paresthesias	2.4	
Sleep disorder	2.1	
Gastrointestinal	29.6	2.9
Nausea	9.6	
Abdominal pain	3.2	
Dyspepsia	3.1	
Vomiting	3.1	
Diarrhea	2.1	
Dry mouth	2.1	
Generalized	28.7	0.4
Fatigue	5.9	
Hypoesthesias	3.5	
Sweating	2.9	
Asthenia	2.7	
Chest pain	2.6	
Fever	0.2	
Respiratory	17.9	0.2
Musculoskeletal	10.8	?
Dermatologic	8.8	?
Urogenital	7.1	0.3
Laboratory abnormalities	0.9	0.4

? = unknown.

reentrant tachycardia.[22] The drug terminated the arrhythmia in 5 and prevented reinduction in each patient. A reduction in retrograde conduction through the fast atrioventricular nodal pathway was seen.

Adverse effects: Initial studies with moricizine using doses of <600 mg/day reported very few adverse effects, and these were primarily gastrointestinal.[12,13] In the dose-ranging, placebo-controlled trials in which >600 mg/day were administered, adverse effects were more common.[14] The most frequent were nausea (11%), dizziness (9%), abdominal discomfort (11%), weakness (4%), headache (3%), constipation (2%), dry mouth (2%) and blurred vision (2%). More serious side effects, usually resulting in drug discontinuation, were arrhythmia aggravation (4.2%), conduction abnormalities (2.5%), anxiety or depression (1.7%) and dizziness and syncope (1.7%). The U.S. data base, which includes 1,256 patients, reported that 71.5% of subjects had at least 1 adverse effect during the follow-up period which was up to 2 years[23] (Table III). However, the drug was discontinued in only 9% of patients, most often because of neurologic or gastrointestinal toxicity. The most frequent adverse effects were neurologic (dizziness, headache, fatigue, hypesthesia, asthenia, nervousness, paraesthesias and sleep disorder); gastrointestinal (nausea, abdominal pain, dyspepsia, vomiting, diarrhea and dry mouth); generalized complaints; respiratory complaints; musculoskeletal problems; and dermatologic and urologic problems. Drug fever, reduced platelet counts and liver function test abnormalities were rarely observed.

In the U.S. data base, the reported incidence of arrhythmia aggravation was 3.2%. In half of these cases, this represented a new sustained ventricular tachyarrhythmia, whereas in the remaining half, there was a statistically significant but nonserious increase in VPCs or runs of nonsustained VT. However, in a group of patients with significant heart disease presenting with serious ventricular tachyarrhythmias, the incidence of arrhythmia aggravation was 11%.[24] In the U.S. data base, congestive heart failure during therapy was observed in 7.1% of patients, but was probably or possibly due to the drug in only 2%.[25] The majority of patients with this adverse reaction had a previous history of congestive heart failure. A similar incidence of heart failure has been observed among patients with a history of a sustained ventricular tachyarrhythmia.[26]

Conclusion: Moricizine is a new antiarrhythmic agent with electrophysiologic properties similar to those produced by other class 1 antiarrhythmic agents. At doses of 600 to 1,200 mg/day it is effective for the suppression of spontaneously occurring VPCs, couplets and runs of nonsustained VT. It is less effective in patients presenting with a sustained ventricular tachyarrhythmia, especially when significant left ventricular dysfunction is present. Although there are few direct comparisons with other antiarrhythmic agents, efficacy rates with moricizine appear to be lower than those reported with drugs that are more potent. An important advantage is less frequent nuisance side effects when compared with other agents. More serious adverse effects (primarily cardiac) do occur, but are less common than with other agents. Moricizine appears to be safe in postinfarction patients and is not associated with the increased mortality seen with encainide and flecainide. Its safety and low incidence of adverse effects are important advantages; however, it is as yet unknown if this drug will reduce the risk of sudden death in postinfarction patients or in any other group, especially those surviving out of hospital sudden death. Therefore, the answer to the question "Is it unique?" awaits the results of CAST-II.

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Medical, Ethical and Legal Issues Regarding Thrombolytic Therapy in the Jehovah's Witness

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We recently cared for a patient who received thrombolytic therapy for an acute myocardial infarction. The patient was a Jehovah's Witness and subsequently had a hemorrhagic death, refusing blood transfusion. The case raised several questions about the medical, ethical and legal considerations involved with the use of thrombolytic therapy in Jehovah's Witnesses and other patients who refuse blood transfusions a priori.

The patient was a 57-year-old woman who presented to a local emergency room complaining of chest discomfort. An electrocardiogram was consistent with an acute inferior myocardial infarction and the patient consented to participate in the Thrombolysis and Angioplasty in Myocardial Infarction 5 investigation. She was randomized to receive thrombolysis with both tissue plasminogen activator and urokinase followed by acute cardiac catheterization. Her initial hemoglobin was normal and thrombolytic therapy was administered within 6 hours from the onset of the symptoms. The patient was a practicing Jehovah's Witness and clearly stated an objection to the use of any blood products in her care. Several days later, she became progressively hypotensive. The patient's stool was melenic and her hematocrit was 20%. After being advised that her clinical condition was life-threatening, the patient again refused the administration of blood or blood products.

Gastrointestinal bleeding continued despite treatment with both sucralfate and an H_2 blocker; her he-

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TABLE I Contraindications to Thrombolytic Therapy

- Absolute
  - Active internal bleeding
  - Cerebral vascular accident (within 2 months) or active intracranial process
- Major relative
  - Recent major surgery
  - Recent serious gastrointestinal bleeding
  - Recent serious trauma
  - Severe hypertension
- Minor relative
  - Infective endocarditis
  - Pregnancy
  - Age >75 years
  - Diabetic hemorrhagic retinopathy
  - Minor trauma including cardiopulmonary resuscitation
  - High likelihood of left-sided thrombus
  - Hemostatic defects

matocrit decreased to 14%. The patient's mental status deteriorated. As she became incapable of making competent decisions, her family voiced concordance with her prior decision to refuse blood transfusions, knowing that she could die without this therapy. Progressive hypotension with concomitant myocardial ischemia ensued which was unresponsive to intravenous fluids and vasopressors and she died.

Medical considerations: There is general agreement that rapid reperfusion of ischemic myocardium is optimal treatment of an acute myocardial infarction. Whereas several methods exist to achieve reperfusion (emergent surgery, angioplasty and thrombolytic therapy), thrombolytic therapy appears to be the best method in the acute setting.[1–4] Other reperfusion techniques, such as coronary angioplasty, are typically appropriate as delayed, rather than acute interventions.[5] Our patient met accepted criteria for using thrombolytic therapy since she had electrocardiographic evidence of an acute myocardial infarction soon after the onset of chest pain. Because her infarction was diaphragmatic and she was hemodynamically stable, however, her prognosis was excellent and the benefits of reperfusion were at least questionable.[6] In fact, in one series, patients subcategorized as having diaphragmatic infarctions were not afforded significant improvement in mortality with thrombolytic therapy.[3] Nonetheless, another trial reported a significant reduction in mortality in these patients.[7] Although diaphragmatic infarctions can be hemodynamically poorly tolerated and result in death, patients with such infarctions generally have a lower mortality rate than those with anterior infarctions. In retrospect, these considerations may have deserved a greater role in the decision to enroll this patient in a protocol involving the use of thrombolytic therapy.

Contraindications to treatment with thrombolytic therapy can be classified as absolute, major relative and minor relative (Table I).[1,8] Several of these contraindications exclude patients who may especially be prone to bleeding complications or who are at considerable risk if bleeding occurs.

Significant bleeding complications from thrombolytic therapy are generally believed to be "rare."[4,9] Although the type and amount of thrombolytic therapy administered plays some role in the incidence of complications, it appears that such therapy carries an approximate 8% risk of major hemorrhagic complications.[9,10] For instance, some data suggest that bleeding episodes are more frequent in patients who receive streptokinase than in those receiving tissue-type plasminogen activator.[11] Additionally, invasive procedures, older age and female gender are associated with an increased risk of bleeding.[9] However, an accurate estimate of mortality in patients who did not receive blood transfusion for life-threatening hemorrhages is not known and would be difficult if not impossible to obtain.

Our patient was enrolled in a multicenter trial examining the effectiveness of combined tissue-type plasminogen activator and urokinase versus each of these agents alone in the treatment of myocardial infarction. After informed consent, she was randomized to receive combination therapy with urokinase and tissue-type plasminogen activator. In a preliminary analysis of patients enrolled in these trials, 15% had gastrointestinal bleeding, but patients who received combination therapy with urokinase and tissue-type plasminogen activator had significantly less bleeding than those who received either agent alone.[12] Nonetheless, our patient had a pronounced blood loss. Her clinical condition was exacerbated by both her own and her family's adamant refusal of all blood products in her care — measures that might have been lifesaving.

Our case raises several questions regarding the use of thrombolytic therapy in a Jehovah's Witness or in any patient who refuses blood transfusion a priori. If thrombolytic therapy is "medically" indicated, should a refusal of blood products be a relative contraindication to its use? If cardiac catheterization can be performed within 3 to 4 hours after the onset of ischemia, should it be used to define the presence or absence of thrombus in order to avoid unnecessary use of a thrombolytic agent? Should the infarction site, size or degree of acute hemodynamic compromise, or a combination of all these be factors in the decision for thrombolytic therapy?

Ethical considerations: Should a Jehovah's Witness who refuses blood transfusion be offered a treatment known to have a risk of bleeding? The ethical principles in conflict here are the physicians' duties of nonmaleficence and respect for autonomy. The principle of nonmaleficence encompasses the physicians' obligation to avoid harming patients as a result of treatment. The principle of autonomy recognizes that the patient is one who chooses in accordance with his/her own values without interference or coercion. John Stuart Mill argued that control over an individual's actions is legitimate only if it is necessary to prevent harm to others. In all other matters, "the individual is sovereign" and free to choose courses of action others may think ill advised, or even foolish.[13]

In the medical setting, the principle of autonomy finds its most insistent expression in the doctrine of informed consent for both experimental protocols and clinical practice.[14] The specific elements of informed consent (disclosure of information, risks and options, the competence or decision-making capacity of the patient or subject, and the voluntariness of the choice) are the concrete embodiments of the autonomy principle in the realm of medicine.

Our case stretches the notion of informed consent to cover not only the the administration of blood products, but also the offering of thrombolytic therapy which may increase the need for blood products. Such therapies must be explained to all patients, including Jehovah's Witnesses, as remedies that are preferable on other grounds (e.g., cardiac outcome), but which make choices about blood products more likely. It obviously matters whether the risk of bleeding is great or small. In this case, the risk was judged to be small, making the choice to offer thrombolytic therapy a reasonable one.

In emergency situations when the patient is incapable of making decisions, physicians are guided by the principle of beneficence and are expected to do what they believe will offer the patient the best chances of survival. However, when circumstances allow, full disclosure and discussion should be the norm. To exclude automatically all Jehovah's Witnesses who may express an objection to blood products from receiving thrombolytic therapy would be to undermine their freedom to choose.

A review of Jehovah's Witnesses' rationales for the refusal of blood transfusions can be found elsewhere.[15] Care must be taken not to treat all Jehovah's Witnesses as uniform adherents to a single monolithic belief. Whereas the authenticity and sincerity of Jehovah's Witnesses who refuse blood products should not be challenged, ambivalence by some Jehovah's Witnesses has been noted. Specifically, some Jehovah's Witnesses seem to indicate a willingness to be coerced, so that blood products may be received so long as it is noted to be contrary to their wish or against their will.[16] Strategies that maximize these possibilities may themselves be morally problematic, yet foreclosing on these options in advance by not offering thrombolytic agents at all would be discriminating against Jehovah's Witnesses, especially if there were no other contraindications to thrombolytic therapy. To make the refusal of blood products equivalent to the refusal of thrombolytic therapy is to confuse the issues. To exclude Jehovah's Witnesses, categorically from thrombolytic therapy would be a mistake of both logic and ethics. Logically, it is a hasty generalization. Ethically it threatens to substitute an unwarranted medical (or legal) paternalism for patient autonomy.

Patients can achieve autonomous decision-making only if supported and protected by physicians and other health care professionals. Respect of patients requires full disclosure about the options regarding available medical treatments, including thrombolytic therapy.

Legal considerations: The issue of blood transfusions in Jehovah's Witness has been argued in the courts for some time and several legal precedents exist.[17,18] The case presented raises the question of whether a physician who withholds thrombolytic therapy from a Jehovah's Witness is at legal risk. The legal principles involved in answering the question are those that govern the treatment of all medical patients and include: the physician's duty to treat the patient, the standard of care, the physician's duty to provide adequate informed consent, the patient's right to refuse treatment, and the State's interest in preserving life.

A physician who undertakes treatment of any patient enters into an implied contract to provide continued medical care as long as it is required.[19] Before undertaking treatment, however, a physician has the option to reject care of the patient and avoid the implied contract. Nonetheless, once care commences, the obligation to continue care can only be dispensed with in one of three ways: (1) the conditions that required immediate treatment cease to exist, (2) a competent patient discharges the physician, or (3) the physician withdraws from the case after providing the patient with reasonable notice and an adequate substitute source of care.[20,21] Under the circumstances of our case an obligation to provide necessary medical treatment for the patient existed from the time of entry into the research study until her death.

The physician has a legal obligation to meet the standard of care in all cases. The standard of care is set by treatment generally accepted and provided by the surrounding medical community.[22] If one assumes that thrombolytic therapy is the standard of care, then withholding it exposes the physician to potential liability. The physicians's determination of the risk of bleeding complications from thrombolytic therapy in a particular clinical setting (to a reasonable degree of medical certainty) provides a sound basis for withholding treatment that might otherwise be considered standard of care. Thus, the standard of care is not absolute, and the particular circumstances of each case must be taken into account before a course of treatment is selected. If thrombolytic therapy is not an "absolute" standard, reasonable alternatives to this treatment should be offered to the patient. Although current research seems divided about the absolute value of thrombolytic therapy in patients with diaphragmatic myocardial infarctions (thus, the standard of care in our case might be debatable), it is easy to imagine a similar scenario in which there is little question about the indication for thrombolytic therapy.

The doctrine of informed consent assures that the patient participates in the decision making process of medical care. The current legal doctrine of informed consent seems to have developed from a series of negligence cases. In the landmark case, *Schloendorff vs. Society of New York Hospital*, a woman who consented to a pelvic examination under anesthesia had a hysterectomy performed without her consent. The court recognized that: "Every human being of adult years and of sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages."[23] In a subsequent case, the court found that physicians have an additional duty to disclose certain facts concerning a procedure before obtaining consent.[24] The physician's duty to obtain informed consent now includes a comprehensive explanation of the risks, benefits and alternatives available to the patient. The patient has the right both to this information and to refuse treatment. Under the doctrine of informed consent, even if the physician advised the patient that a transfusion might be required after thrombolytic therapy, it would still be the patient's right to decide whether to receive thrombolytic therapy assuming the concomitant risks.[25,26] Our patient gave informed consent for receiving thrombolytic therapy, documented by her signed agreement to participate in the study. Written consent included acknowledgment of the potential for gastrointestinal bleeding possibly requiring blood transfusion. For the competent patient, the right to refuse care or a particular treatment extends to life-saving and life-prolonging treatment. In a 1986 case, a 23-year-old Jehovah's Witness without children was permitted to refuse a life-sustaining blood transfusion and the court held that the patient's rights were paramount.[27] Subsequently, the Supreme Court of Florida upheld the rights of a competent Jehovah's Witness mother to refuse blood transfusion. The court felt that the "State's interest in having children raised by two loving parents was insufficient to overcome [the] patient's right pursuant to practice of her religion, to refuse lifesaving blood transfusions."[28]

Although a constitutional right to religious freedom is recognized, the State has a counterbalancing interest in the preservation of life. As demonstrated in both the *Quinlan* case and the *Saikewicz* case, consideration must be given to whether withholding treatment would be ethically justified under the particular circumstances of each case.[29,30] If the patient seeks hospitalization, but also wishes to limit the course of treatment in a manner inconsistent with accepted medical practice, the physician or hospital would not be required to act in any way that is viewed as unethical. Under these circumstances a physician would have the duty to transfer the patient to the care of a doctor who would undertake treatment consistent with the patient's values. The trend in recent cases has emphasized that patient autonomy governs.[30]

Thus, if thrombolytic therapy is indicated and a blood transfusion does not represent a reasonable risk, then thrombolytic therapy should be administered. If, however, there is relative certainty that thrombolytic therapy will necessitate a subsequent blood transfusion, and a competent patient has stated an absolute refusal to receive blood transfusions, then the physician would be best advised either to act in accordance with the patient's wishes or to transfer the patient to one who could do so.

Perhaps in future instances it would be best to have questions related to blood transfusion emphasized with *any* patient who might object to transfusion before administering thrombolytic therapy. In short, the competent patient must ultimately decide. If the patient is not competent or emergency circumstances exist, the physician is bound to proceed following the standard of care with treatment that appears to best benefit the patient.

Conclusions: A review of the medical, ethical and legal issues involved in the use of thrombolytic therapy in Jehovah's Witnesses emphasizes the need for an informed consent that highlights the possible need for blood transfusion. Physicians caring for a Jehovah's Witness, or any patient who a priori refuses blood transfusion, in similar settings may wish to consider a variety of factors such as the likely hemodynamic consequences of the infarction and the use of treatment modalities that might minimize the need for blood transfusions. Given the current epidemic of human immunodeficiency virus, it is conceivable that other patients may refuse blood transfusion secondary to fear of infection. Additionally, while research continues to assess the efficacy of thrombolytic therapy, it may be prudent to exclude patients from experimental protocols who in advance refuse blood transfusions since this may bias a critical evaluation of the therapy itself with respect to tabulations of morbidity and mortality.

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Coronary Artery Surgery in Octogenarians

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Coronary surgery is being performed increasingly in older patients who may have more extensive disease as well as other factors that may lead to more frequent complications and death.[1-3] Several studies have shown that the rate of complications and mortality in elderly patients are higher than in younger ones.[4-7] Advanced age has also been shown to correlate with late mortality after cardiac surgery.[8] Because of these data, there has been uncertainty as to use of cardiac surgery in older patients especially in those aged ≥80 years. This report presents results of coronary artery bypass grafting both in hospital and at follow-up in patients aged ≥80.

The study population comprised all patients aged ≥80 years who underwent isolated first coronary bypass surgery at Emory University Hospital or Crawford W. Long Hospital between 1978 and 1989. Patients with coexisting valve, congenital heart and primary myocardial diseases, those needing aneurysmectomy, and those undergoing coronary surgery in the setting of unsuccessful angioplasty were excluded from the study. In all, there were 154 patients included in the study. Coronary arteriography was performed with multiple right and left anterior oblique projections using the Judkins technique. All angiograms were interpreted by ≥2 experienced angiographers. Contrast left ventriculograms were obtained in the 30° right anterior oblique projection. Extracorporeal circulation was instituted by standard techniques,[9] and perfusion was maintained at 2.0 to 2.4 liters/min/m^2. Systemic (30 to 25°C) and topical hypothermia, and cold potassium cardioplegia were used for myocardial protection. Cardioplegic solution was reinfused at 20 to 30 minute intervals to maintain an intramyocardial temperature <20°C. Distal anastomoses were formed with the aid of optical magnification. Grafts were created from either internal mammary arteries or vein grafts. Patients were then weaned from cardiopulmonary bypass, and chests were closed using standard techniques. Patients were then transferred to the surgical intensive care unit.

Angina class was defined by the Canadian Cardiovascular Society classification.[10] Variables of previous myocardial infarction, diabetes mellitus and hypertension were gathered from the patient's history. Emergent surgery was defined by the operator. A vessel was considered stenotic if there were ≥50% diameter narrowing of the main coronary artery or of any major branch. The number of vessels diseased was determined by a set algorithm that has been used in this institution.[11] The number of grafts was determined by the number of distal anastomoses. Myocardial infarction after surgery was determined by the development of new Q waves. A neurologic event was a persistent change in neurologic function, including persistent disorientation, after the first several days in the intensive care unit.

All data were prospectively collected and entered into a computerized clinical database. Data are presented as a percentage or mean ± standard deviation, where appropriate. For purposes of analysis, prolonged stay was defined as ≥10 days after coronary surgery. Categorical variables were compared by Pearson's chi-square. Multivariate correlates of in-hospital death were determined by stepwise logistic regression analysis. Statistical testing was performed with BMDP. Patients were followed up by telephone survey. Events occurring during subsequent hospitalizations were obtained from the clinical database. Survival was determined by the Kaplan-Meier method.[12] Differences in survival between groups were determined by the Mantel-Cox method.[13] Multivariate correlates of survival were determined by Cox model analysis.

Mean age of the patients was 82 ± 2 years (range 80 to 89); 98 (64%) were men, 73 (47%) had a prior myocardial infarction, 76 (49%) had hypertension, 26 (17%) had diabetes mellitus, 130 (84%) had class III or IV angina, 19 (12%) had history of congestive heart failure, 103 (67%) had 3-vessel or left main coronary artery disease and 46 (32%) had an ejection fraction <50%. Procedural characteristics and complications

TABLE I Operative Characteristics

	No.
Emergent	41 (27%)
Grafts	3.3 ± 1.0 (1-6)
Internal mammary	16 (10%)
Exploration for bleeding	7 (4.5%)
Intraaortic balloon pump	9 (5.8%)
Q-wave myocardial infarction	4 (2.6%)
Stroke	8 (5.2%)
Hospital death	16 (10%)
Length of stay	11 ± 8 (0-59)

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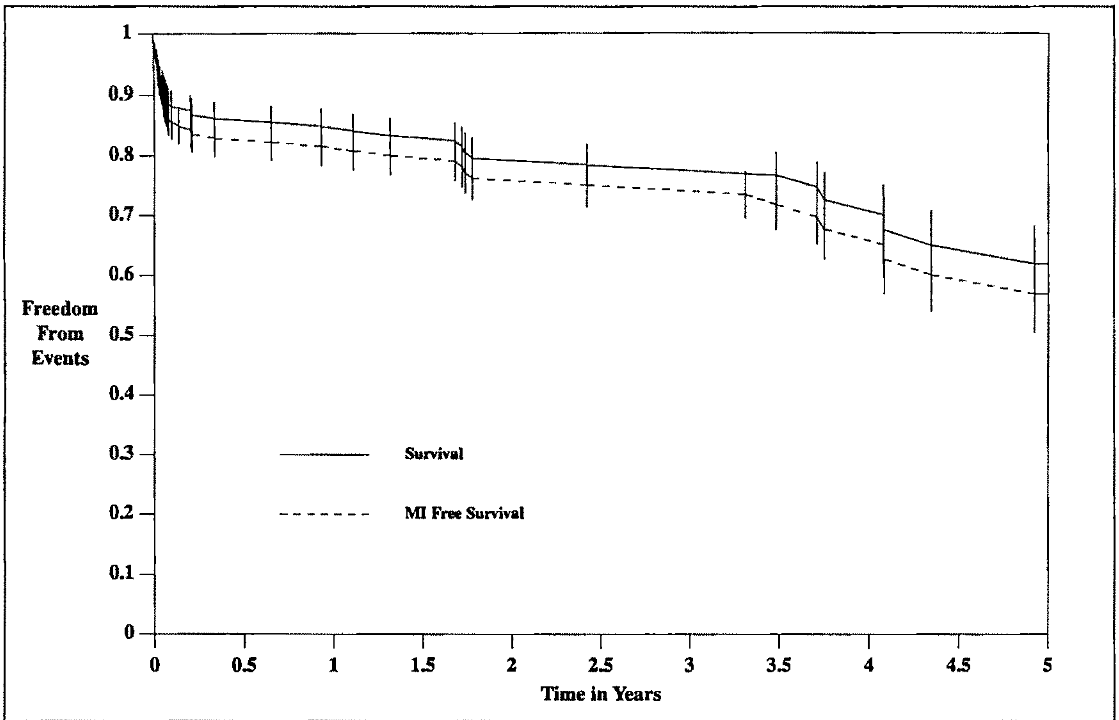
TABLE II Correlates of In-Hospital Mortality

	Total	Deaths (%)	p Value
Diabetes mellitus	26	6 (23)	0.02
Diabetes absent	128	10 (8)	
Ejection fraction <50	46	9 (20)	0.03
Ejection fraction ≥50	96	7 (7.3)	
Ejection fraction <50 and diabetes mellitus	14	4 (29)	0.02
Ejection fraction <50 or diabetes mellitus	43	7 (16)	
Ejection fraction ≥50 and diabetes absent	85	5 (6)	

are listed in Table I. Surgery was emergent, as defined by the surgeon, in 41 patients (27%). Only 16 patients (10%) had had an internal mammary graft. Reexploration for bleeding was needed in 7 patients (4.5%). The intraaortic balloon pump was needed in 9 patients (5.8%). A Q-wave myocardial infarction in the hospital occurred in 4 patients (2.6%), a stroke in 8 (5.2%) and in-hospital mortality in 16 (10%). The length of hospital stay after surgery averaged 11 ± 8 days (range 0 to 59).

Clinical variables were analyzed as correlates of survival, both in the hospital and after discharge. Only diabetes mellitus and left ventricular ejection fraction emerged as significant correlates. In-hospital mortality occurred in 10 of 128 (7.8%) patients without diabetes mellitus, and in 6 of 26 (23%) with diabetes (Table II). Eight of the 26 diabetics were receiving insulin, and 2 (25%) died. Diabetics receiving insulin did not have a higher mortality than those not receiving insulin. In-hospital mortality occurred in 9 of 46 (20%) patients with ejection fractions <50%, and in 7 of 96 (7.3%) with ejection fractions ≥50%. In the 14 patients with ejection fractions <50% and diabetes mellitus, 4 died (29%). In the 44 patients with ejection fractions <50% or diabetes mellitus, 7 died (16%). In the 85 patients with ejection fractions ≥50% and no diabetes mellitus, 5 died (5.9%).

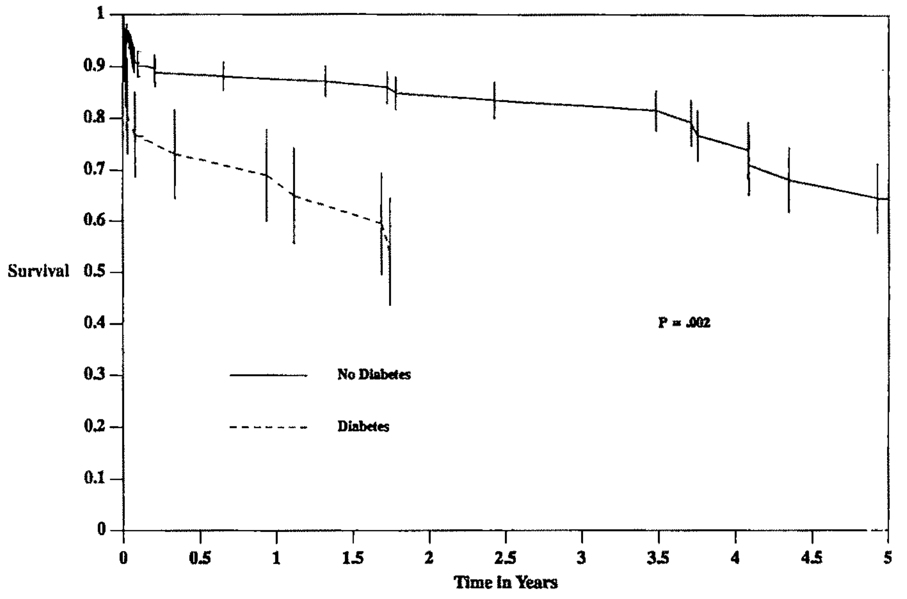
Five-year survival (Figure 1) was 0.62, and 5-year myocardial infarction-free survival was 0.57. Two-year survival was 0.85 without and 0.54 with diabetes mellitus (Figure 2). Five-year survival without diabetes mellitus was 0.64. Two-year myocardial infarction-free survival was 0.81 without and 0.54 with



Death											
N Remaining	152	129	119	99	82	67	53	42	30	25	19
Survival	1	.86	.85	.83	.80	.78	.78	.77	.72	.65	.62
N Events	0	21	23	25	29	30	30	31	33	36	37
Death or MI											
N Remaining	152	124	114	94	77	64	50	40	28	23	17
Survival	1	.83	.82	.80	.76	.75	.75	.72	.68	.60	.57
N Events	0	26	28	30	34	35	35	37	39	42	43

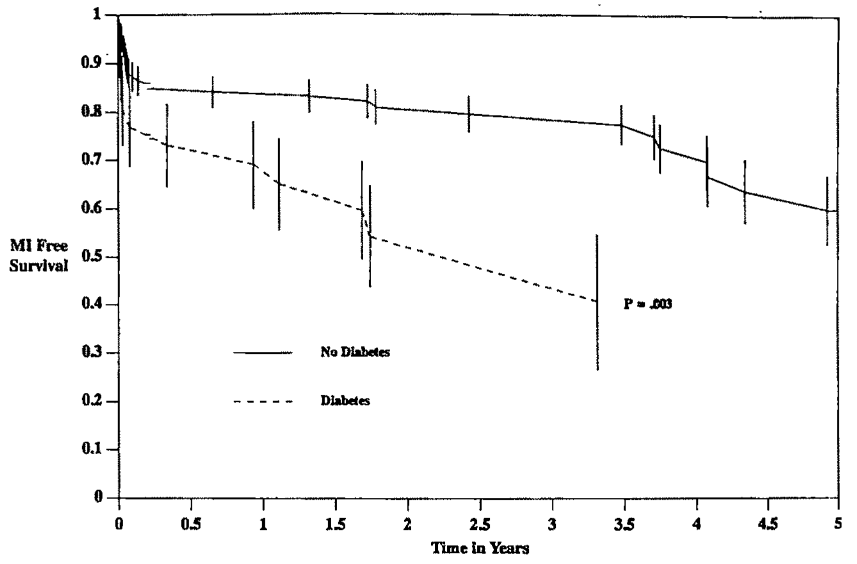
FIGURE 1. Five-year freedom from events in 152 patients. Curves represent survival and myocardial infarction-free survival. MI = myocardial infarction.

diabetes mellitus (Figure 3). Five-year myocardial infarction-free survival was 0.60 without diabetes mellitus. Presence or absence of angina at follow-up was available in 106 patients at an average of 35 ± 22 months after surgery. At the time of follow-up, 87 patients (82%) were free of angina. There was no significant difference in angina status at follow-up between patients with no or mild angina and those



No Diabetes											
N Remaining	126	111	102	86	72	60	47	39	28	23	17
Survival	1	.89	.88	.87	.85	.83	.83	.82	.76	.68	.64
N Events	0	14	15	16	18	19	19	20	22	25	26
Diabetes											
N Remaining	26	18	17	13	10						
Survival	1	.69	.65	.65	.54						
N Events	0	8	9	9	11						

FIGURE 2. Five-year survival in patients with and without diabetes.



No Diabetes											
N Remaining	126	106	97	81	68	57	44	37	26	21	15
Survival	1	.85	.84	.83	.81	.79	.79	.77	.73	.64	.60
N Events	0	19	20	21	23	24	24	25	27	30	31
Diabetes											
N Remaining	26	18	17	13	10	7	6	3			
Survival	1	.69	.65	.65	.54	.54	.54	.41			
N Events	0	8	9	9	11	11	11	12			

FIGURE 3. Five-year myocardial infarction-free survival in patients with and without diabetes. MI = myocardial infarction.

with severe angina originally. Thus, 75 of 101 (82%) patients with severe angina at the time of surgery were without chest pain at follow-up.

The in-hospital and long-term results of coronary bypass surgery in octogenarians are reviewed in this study. In-hospital mortality was 10%, and ejection fraction and presence of diabetes mellitus were correlates. Diabetes mellitus was also a correlate of mortality and the combined end point of mortality and myocardial infarction over the several years after the procedure. Patients without diabetes had lower in-hospital mortality and remarkably high 5-year survival for octogenarians. In addition, 82% of the patients were pain-free during follow-up.

Old age has been shown to be a risk factor for in-hospital and long-term mortality.[4-7] The results of the current study are consistent with reports on geriatric patients from other centers.[14-16] Edmunds et al[14] reported a 90-day mortality in 10 of 41 (24%) patients aged ≥80 years undergoing coronary surgery. Subsequent series have shown improved results. Naunheim et al[15] reviewed the results of coronary and valve surgery in 103 patients aged ≥80 years. As in the present study, symptomatic improvement was noted. Perioperative predictors of mortality were use of the balloon pump before surgery, history of congestive heart failure, and mitral valve replacement. In-hospital mortality occurred in 9 of 71 (13%) patients undergoing coronary bypass surgery. Tsai et al[16] reported results of coronary bypass surgery in 64 patients aged >80 years. Within 30 days, 2 patients (3.1%) died. Of the surviving patients, 60% were symptomatically improved. Percutaneous transluminal coronary angioplasty has also been reported in octogenarians.[17-18] Jeroudi et al[17] reported impressive results in 54 patients, with angiographic success in 49 (91%) and 2 deaths (3.7%) in the hospital. Survival was 81% at 1 year and 78% at 3 years. Restenosis and the need for repeat angioplasty or coronary surgery were limitations. Kern et al[18] cautioned that angioplasty in patients aged >80 years is a high-risk procedure. Selection of appropriate cases limits the ability to compare patients undergoing angioplasty with those treated surgically.

Selection of the appropriate form for therapy in patients aged ≥80 years may be complicated by higher adverse event rates than those in younger ones. Although the influence of age on the cost of surgery is not known, older patients do have a longer mean length of hospital stay.[19] Complications including stroke and wound infections are more frequent in older patients and can result in dramatically longer hospital stays in some patients.[19] The criteria for operating on patients aged ≥80 years are likely to be different than for those who are decades younger, with the severity of angina being more important in the decision to operate on octogenarians. There is almost certainly a tendency to avoid surgery in patients aged ≥80 years. Factors that were not available for this study, such as detailed assessment of the diffuseness of the coronary artery disease on angiographic review, and consideration of how robust or frail the patient is, may further improve selection of appropriate cases. With careful case selection, the probability of successful surgery in octogenarians is increased. Thus, the probability is that selected patients aged ≥80 years will have successful surgery despite higher risks and almost certainly higher costs. It is of interest to note that 5-year survival in 1987 in the United States for all persons aged 80 to 85 years was 66%,[20] which is quite close to the 62% found in this study. Whether life is prolonged and whether coronary surgery can be cost-effective in patients aged ≥80 years cannot be answered from the current literature. Although the current crisis in health care costs may result in attempts to deny certain procedures to the elderly, this report suggests that coronary artery bypass surgery should not be denied to patients on the basis of age alone.

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Prevalence and Significance of ST-Segment Alternans During Coronary Angioplasty

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Electrical alternans is a phenomenon of alternating electrocardiographic morphology on an every-other-beat basis. ST-segment alternans is often seen in the animal laboratory with subtotal or transient coronary artery occlusion.[1] In humans it has been observed in a variety of settings, such as Prinzmetal's angina and once during percutaneous transluminal coronary angioplasty (PTCA).[2] Although clinically rarely observed, ST-segment alternans has been correlated with subsequent malignant arrhythmias and may be an important marker of electrically unstable myocardium.[3] This study was performed to determine whether PTCA-induced transmural ischemia could reproducibly induce ST-segment alternans and serve as a model for this syndrome.

Laboratory records of 407 consecutive patients undergoing PTCA, with continuous electrocardiographic monitoring and recording of ≥2 standard leads during balloon inflations, were evaluated. Lead selection was based on the most likely ischemic zone during PTCA. Most procedures were performed using standard over-a-wire balloon techniques with arterial and, when feasible, intracoronary blood pressure monitoring. More than 90% of the patients had ≥1 balloon inflation >60 seconds. Each patient's record was reviewed for target arteries, number and duration of balloon inflations, presence of ST-segment alternans, and complications.

Five patients were observed to have ST-segment alternans. Their records were further reviewed for cardiac history, prior PTCA procedures, coronary anatomy and ventricular function, medications and electrolytes. The records were also reviewed for contrast agent use, anginal symptoms, hemodynamic changes and sequence of electrocardiographic changes in relation to duration of balloon inflation.

Clinical characteristics and pertinent data for the 5 patients with ST-segment alternans are listed in Table I. Four of these cases occurred of 195 angioplasties of the left anterior descending artery, and 1 of 102 angioplasties of the left circumflex artery. No episodes of ST-segment alternans were seen in 110 angioplasties of the right coronary artery. ST-segment alternans never developed with <55 seconds of arterial occlusion. With repeated dilatations, ST-segment alternans was reproducible at about the same time of balloon occlusion. RR intervals and QRS morphologies were unchanged during periods of ST-segment

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TABLE I Clinical Characteristics of Patients with ST-Segment Alternans During Coronary Angioplasty

Pt. No.	Age (yr) & Sex	PTCA Artery	Collaterals	Diameter Narrowings in Other Coronary Arteries	Onset of Alternans (sec)	Type of ST Change	Inflation Time (sec)	Anginal Symptoms
1	71 M	LAD	0	90%–D1	55	E	180	Moderate
2	74 M	LAD	0	60%–LC	95	E	180	—
3	71 F	LAD	+	100%–LC	60	E	420	Slight
4	57 M	LC	0	0	120*	E	360	Severe
5	69 M	LAD	+	95%–LC	100	D	180	Slight

*Persisted for 120 seconds, then developed into uniform ST elevation.
D = ST-segment depression; D1 = first diagonal branch; E = ST-segment elevation; LAD = left anterior descending artery; LC = left circumflex artery; PTCA = percutaneous transluminal coronary angioplasty; — = no information available.

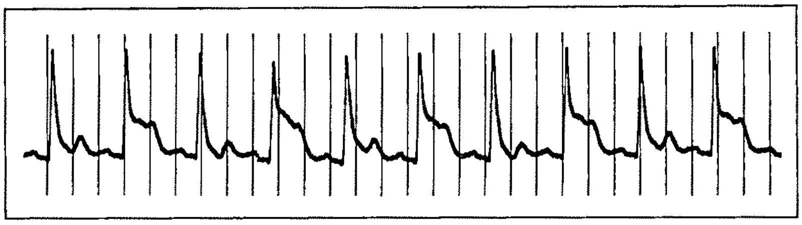

FIGURE 1. An example of ST-segment alternans as recorded from patient 3 on electrocardiographic lead V_5 at 25 mm/s.

alternans (Figure 1). Pulsus alternans was not noted by either arterial or intracoronary blood pressure monitoring, whereas the perception of angina ranged from minimal to severe during the period of ST-segment alternans. All patients described in this report had normal electrolytes and QT intervals. All patients were pretreated with both nitrates and calcium antagonists (nifedipine or diltiazem). The procedures were performed with a variety of contrast agents (iohexal, and diatrizoate and ioxaglate meglumine sodiums). Patient 4 had previous PTCA at the same site without ST-segment alternans, but balloon inflation times then were <50 seconds. Patient 5 was observed to have ST-segment alternans only during a 1-balloon inflation in a distal left anterior descending artery lesion. This lesion was the first of 3 lesions dilated. ST-segment alternans was not observed during later inflations of a more proximal left anterior descending or left circumflex artery stenosis. All PTCAs were successful, with no complicating ventricular arrhythmias or evidence of myocardial damage.

ST-segment alternans is a poorly understood syndrome that may be an important marker for ischemic myocardium at risk for malignant ventricular arrhythmias.[3] Clinically, it may not be apparent on the surface electrocardiogram, because it can be a very localized phenomenon.[4] Transmembrane action-potential alternans can be demonstrated at the cellular level between ischemic and normal myocardial cells.[5] In the dog model, ST-segment alternans is associated with a threshold decrease in coronary blood flow and with alternating levels of left ventricular function, with the most ischemic-appearing complexes resulting in the greatest left ventricular output.[6,7] The present report and other studies in humans[2,4] have shown no hemodynamic alterations during ST-segment alternans. These findings need further confirmation with either echocardiographic or catheter tip transducer techniques.

ST-segment alternans in our patients occurred only during relatively prolonged balloon dilatations. This suggests that a threshold of ischemia may be required to induce ST-segment alternans. Presence of demonstrable collaterals in several patients, and their ability to tolerate prolonged balloon inflations, implies that ST-segment alternans may be less ischemic in response than progressive ST-segment elevation. ST-segment alternans may be part of the continuum of ST-segment responses to transmural myocardial ischemia. This hypothesis is supported by the observation of ST-segment alternans progressing to uniform ST-segment elevation.

This study suggests that ST-segment alternans is a relatively rare phenomenon during PTCA and occurs without significant sequelae. Extensive use of calcium antagonists in these patients may be suppressing the manifestation of ST-segment alternans.[7] Alternans may have been too localized to distinguish with standard electrocardiography. Monitoring 12-lead electrocardiograms, orthagonal leads, intracoronary electrodes or monophasic action potentials may have yielded a greater prevalence of this phenomenon.

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Echocardiographic Documentation of Splenic Anatomy in Complex Congenital Heart Disease

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Splenic abnormalities are associated with complex, cyanotic congenital heart disease (CHD).[1,2] Patients with abnormal spleens may also have an increased susceptibility to infection,[3,4] or additional characteristic gastrointestinal anomalies.[2] For these reasons, it is important to routinely define the splenic status of patients with complex CHD. In the past, determination of splenic status needed either radiation exposure (computed tomography or radionuclide imaging)[5,6] or indirect evidence from blood smears (presence or absence of Howell-Jolly bodies).[1,7] Ultrasonography can image the spleen consistently and clearly.[8] Routine ultrasonic imaging of the spleen as a part of a comprehensive echocardiographic examination has not been reported. This study reports our recent experience with routine visualization of the spleen during complete echocardiographic examinations of patients with complex CHD.

We retrospectively reviewed the records of 57 patients who had a comprehensive echocardiographic evaluation for cyanotic CHD between May 1989 and January 1990 (8 months). Data were recorded regarding the results of routine echocardiographic imaging of the spleen, cardiovascular anatomy and ultimate outcome. Results of the echocardiographic examination were compared with available hematologic, radiographic and autopsy documentation of splenic status.

To examine the spleen, the abdominal situs and position of the liver and stomach were determined from subcostal abdominal scans (Figure 1).[9] The transducer was then transferred to the flank, posterior to the previously identified stomach. When a spleen was present it was invariably located posterior and lateral to the stomach, and superior to the kidney.[1,10,11] Scans from the flank demonstrated the spleen to be a distinct, homogeneous granular organ without the portal vascular pattern that is characteristic of the liver. Another feature that in our experience differentiated the spleen from the liver was that hepatic tissue was never imaged posterior and lateral to the stomach with this technique. The spleen was considered normal when it was single and found in the previously described location (Figure 2). Polysplenia was diagnosed when there were multiple discrete areas of splenic or septated splenic tissue imaged in the appropriate location (Figure 3). The examination was consistent with asplenia when no areas with splenic characteristics could be identified.

Mortality rates in the 3 groups of patients were compared using chi-square analysis. Only p values ≤ 0.05 were considered significant.

Echocardiography could be used to make a diagnosis of splenic status in each case. The spleen was

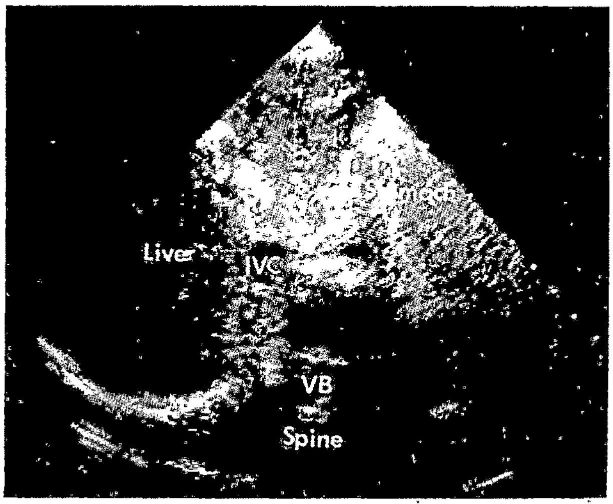

FIGURE 1. Normal subcostal (abdominal) short-axis scan demonstrating gas-filled stomach that obscures posterior structures. IVC = inferior vena cava; VB = vertebral body.

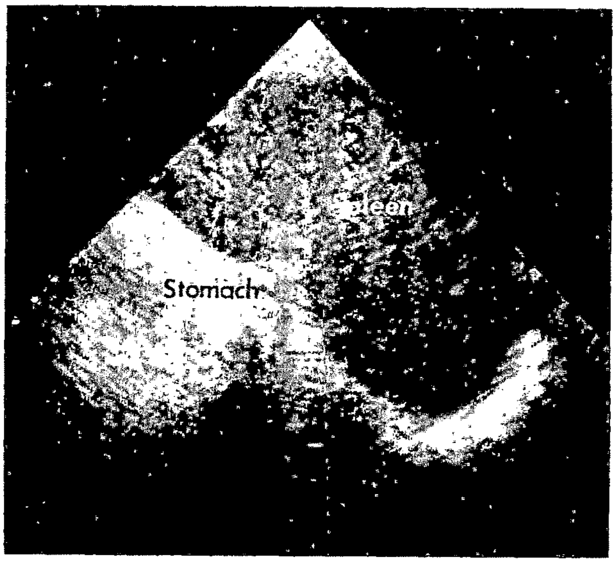

FIGURE 2. Image from posterior left flank demonstrating normal spleen.

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echocardiographically normal in 32 patients. Although normal, it was right-sided in 2 patients. The patients with normal spleens had a mean age of 6 years (range 1 day to 25 years). Polysplenia was diagnosed by echocardiography in 11 patients, and no splenic tissue could be identified in 14 (asplenia). Patients with polysplenia had a mean age of 6 years (range 6 months to 13 years). Asplenic patients had a mean age of 13 years (range 4 to 31).

Patients with normal spleens had various cardiac malformations (Table I). All 11 patients with polysplenia had interruption of the inferior vena cava, with either azygous or hemiazygous continuation and independent hepatic vein drainage. Ten of these patients also had a complex form of single ventricle. The eleventh patient had complex double-outlet right ventricle. All 14 patients with asplenia had a form of complete atrioventricular canal defect with a functional single ventricle and pulmonary valve stenosis or atresia. Thirteen of these patients also had anomalous pulmonary venous connections.

Fourteen of the 43 patients with echocardiographically detectable splenic tissue had blood smears. Howell-Jolly bodies were absent in every case. Ten of the 14 asplenic patients had blood smears. All of these smears were positive for Howell-Jolly bodies. Fifteen patients underwent another diagnostic study that provided information on splenic anatomy (14 computed tomographic or magnetic resonance scans and 1 autopsy). Eleven other imaging studies were able to determine splenic status, and 4 studies were inconclusive. When these examinations were able to conclusively define splenic status, the findings always agreed with the echocardiographic description of the spleen.

Fifty-four of the 57 patients in this study had a subsequent cardiovascular operation. Twenty-nine patients with normal spleens underwent surgery. There were 3 nonsurviving patients in this group (mortality 10.3%). All patients with polysplenia and asplenia underwent surgery. All 11 patients with polysplenia survived surgery. There was 1 nonsurviving patient in the group with asplenia (mortality 7.1%) who died secondary to sepsis. None of the other deaths were related to infection.

There were 6 late deaths in the 50 initial surviving patients. Two patients had normal spleens, 1 had polysplenia and 3 were asplenic. Two of the 3 late deaths in the group with asplenia were secondary to sepsis. None of the other deaths were related to infection.

The only statistically significant difference in outcome was in the group with asplenia. Even with antibiotic prophylaxis, these patients had a significantly higher rate of infection-related death (p = 0.01) than did those with normal spleens. The group with polysplenia was too small to allow a valid statistical comparison.

TABLE I Cardiovascular Malformations in Patients with Normal Spleens*

Malformation	Number of Patients
Univentricular heart	11
Complete transposition of the great arteries	6
Pulmonary atresia with VSD	5
Pulmonary atresia with intact ventricular septum	2
Complete AV canal with tetralogy of Fallot	2
Complex double-outlet right ventricle	2

*One patient had each of the following: tetralogy of Fallot; complete AV canal with hypoplasia of the left ventricle; tricuspid atresia; and truncus arteriosus.
AV = atrioventricular; VSD = ventricular septal defect.

Defining the splenic status of patients with complex CHD is clinically important for several reasons. Patients with asplenia are at higher risk of sepsis from encapsulated bacteria.[3,4] Even with prophylaxis, the rate of infection-related death in our patients with asplenia was greater than it was in those with normal spleens. The fact that all of these patients had major surgery during the study period may, in part, explain the persistent risk of sepsis. Compliance may also have played a role. Regardless of the explanation for this finding, when asplenia is diagnosed, daily antibiotic prophylaxis should be prescribed to decrease the risk of sepsis.[12] Additionally, presence of an abnormal spleen may suggest the coexistence of associated anomalies of the cardiovascular and gastrointestinal systems.[1,2]

The spleen and splenic anomalies can be confidently identified during a comprehensive echocardiographic examination. In this series of 57 patients with complex CHD, the echocardiographic diagnosis of splenic status was confirmed in every case in which complimentary studies were available.

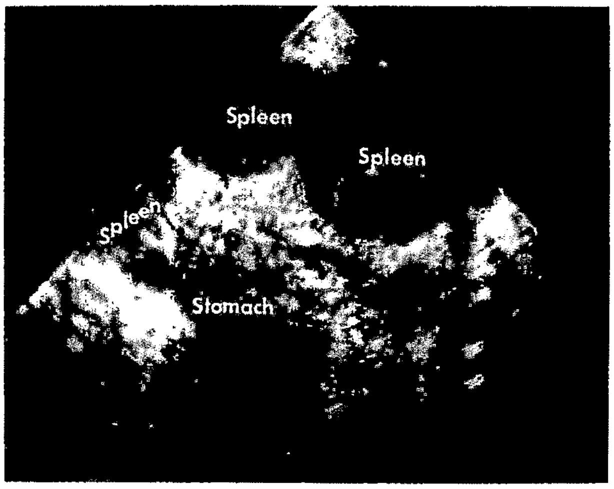

FIGURE 3. Image from posterior left flank demonstrating polysplenia.

Echocardiographic screening for splenic anomalies is convenient and accurate, and avoids radiation exposure. When results of echocardiographic screening are combined with those of a blood smear, the clinician obtains a complete anatomic and functional assessment of splenic status. We recommend that splenic imaging be included as a routine part of the complete echocardiographic evaluation of patients with complex CHD.

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Frequency of Positive Blood Cultures During Transesophageal Echocardiography

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Although recommended for a number of diagnostic and therapeutic procedures in patients at increased risk for infective endocarditis, antibiotic prophylaxis is generally not considered necessary for upper gastrointestinal endoscopy.[1,2] Thus, the recent recommendation for antibiotic prophylaxis in transesophageal echocardiography[3] is somewhat surprising. With the increasing number of transesophageal examinations, the matter clearly needs the cardiologists' attention. In this article, we report on the incidence and nature of positive blood cultures and smear samples from the echo probe of patients undergoing transesophageal echocardiography in our department.

In 144 consecutive patients undergoing transesophageal echocardiography because of central neurologic disorders, blood samples were drawn for blood cultures before (= 0 minutes), during (= 15 minutes) and after (= 30 minutes) the procedure. In 27 of these patients, smear samples of the echo probe were additionally taken before and after the intervention. In a control group of 40 patients without transesophageal echocardiography, blood was obtained for cultures at the same time intervals.

After thorough skin disinfection with 70% isopropanol, an indwelling cannula with a 3-way stopcock was placed in the cephalic vein. The 3 blood samples were each taken from a different disinfected outlet of the 3-way stopcock. Alcohol rather than iodine disinfection was chosen to make our results comparable to those of Görge et al.[3] *Skin antisepsis is identical with both methods.*[4] *Our purpose in drawing blood samples with an indwelling cannula rather than a new phlebotomy each time was to reduce the possibility of local contamination through subsurface skin bacteria. The blood samples were cultured in aerobic (supplemented brain heart infusion) and anaerobic (thioglycollate medium) liquid media with further subculture on chocolate, MacConkey and malt agar. Smear samples were placed in sterile tubes with culture media. Processing of blood cultures and smear samples followed standard microbiologic procedures.*

All patients were hospitalized at the time of the investigation. Exclusion criteria were acute or chronic infections, immunologic disorders, antibiotic or immunosuppressive medication or invasive procedures within the previous 3 weeks. A 2-week follow-up included daily physical examinations with rectal temperature readings and 3 blood counts. A further physical examination was performed after 6 months.

Of a total of 864 blood cultures from patients undergoing transesophageal echocardiography, 34 (3.9%) were positive with facultative pathogenic bacteria in 31 (Table I). Substracting the 6 cultures already found positive before the intervention leaves 28 positive cultures (3.2%) during or after the procedure. All smear samples were sterile before the intervention

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and showed moderate growth of local bacteria afterward. Only 1 patient had the same pathogen (S. epidermidis) in both the blood sample and the probe smear after transesophageal echocardiography (patient 2 in Table II). In the control group, 6.3% of the blood cultures were positive. During follow-up, no patient developed signs of bacterial infection.

For a number of reasons, we find it unlikely that these positive blood cultures truly reflect intervention-induced bacteremia: The incidence of positive blood cultures was not higher during or after transesophageal echocardiography than in our control group. Contamination of blood cultures is reported to be between 3.8 and 8.2%,[5] a rate consistent with the 3.4 and 6.3% incidence of positive blood cultures found in this study. Only 1 patient had the same pathogen (S. epidermidis) in both the smear from the echo probe and the blood culture. A 6-month follow-up showed no clinical manifestation of bacteremia.

A comparable study on blood cultures during transesophageal echocardiography published by Görge et al[3] was stopped after positive blood cultures were found in 4 of 24 patients. In a study different from ours, 2 blood samples were taken before and another 2 during the intervention and a venipuncture was performed at a different site for each blood sample. Because all of the blood cultures obtained before the intervention were sterile, the authors suggest that they truly detected intervention-induced bacteremia and that antibiotic prophylaxis should precede transesophageal echocardiography. A number of points seem noteworthy in this study: The sterility of all preinterventional blood cultures can only be a chance finding. Studying the bacterial flora of the antecubital fossa before and after alcohol disinfection, Evans and Mattern[6] found a surviving bacterial population in 9 of 25 subjects after disinfection, probably due to the subsurface localization of some skin bacteria in sebaceous canals or under keratinized epithelial cells or debris.[7] In the 4 patients with positive blood cultures, bacterial growth was always detected in both blood samples drawn during transesophageal echocardiography. Only 1 patient, however, had the same bacteria (S. epidermidis) in both cultures. In the other 3 cases, 2 or 3 different bacteria were detected in the 2 blood samples of the same patient. Because the authors state that they have demonstrated bacteremia in these cases, they actually suggest that their patients had intervention-induced bacteremia with 2 or 3 different strains of bacteria. They also took throat smears, but only report the findings for patients with positive blood cultures. After the authors' reasoning, the 8 different bacteria detected in these blood cultures should have originated in the throat, yet only 3 were actually found in the throat smears of the same patients.

Two other investigations recently reported an incidence of bacteremia during and after transesophageal echocardiography of 3.2 and 4.2%, respectively[8,9]; all positive blood cultures were considered contaminants. In summary, neither these studies nor ours or the one by Görge et al[3] have shown an incidence of bacteremia higher than the expected contamination rate.

TABLE I Positive Blood Cultures and Bacteria

	TEE (n = 864)*			Control (n = 240)*		
	0 Min	15 Min	30 Min	0 Min	15 Min	30 Min
S. coag. neg.	4	10	5	5	2	3
Propionibacterium		6	5		3	1
Corynebacterium		1				
Aerococcus viridans†	1					
Enterobacter spec.†	1					
Acinetobacter†		1				
Enterococcus avium				1		
Total (n)	6	18	10	6	5	4

*0 Min, 15 Min, 30 Min = blood samples taken before (0), during (15) or after (30) transesophageal echocardiography.

†Usually laboratory contaminants.

Number of positive blood cultures and bacteria found in 144 consecutive patients undergoing transesophageal echocardiography and in 40 control patients without transesophageal echocardiography.

coag. = coagulase; n = number of blood samples analyzed in each group; neg. = negative; S. = staphylococcus; spec. = species; TEE = transesophageal echocardiography.

TABLE II Smear Samples of the Echo Probe and Positive Blood Cultures

Pt. No.	Blood Culture	Smear Probe After TEE
1	Propionibacterium after 7 days, BC 30′	S. viridans S. epidermidis
2	S. epidermidis after 7 days, BC 30 min.	S. epidermidis S. viridans
3	S. epidermidis after 7 days, BC 0 min.	S. viridans Neisseria
4	S. epidermidis after 5 days, BC 15 min.	S. viridans Neisseria
5	Propionibacterium after 4 days, BC 15 min.	S. viridans S. epidermidis

Smear samples of the echo probe and blood cultures in patients undergoing transesophageal echocardiography with positive blood cultures (5 of 27; see text for details).

BC = blood cultures taken before (0 minutes), during (15 minutes) or after (30 minutes) transesophageal echocardiography; S. = staphylococcus or streptococcus; TEE = transesophageal echocardiography.

Antibiotic prophylaxis of infective endocarditis is not recommended for upper gastrointestinal endoscopy without biopsy.[1,2] In an evaluation of 41 prospective studies of endoscopy-induced bacteremia, Botoman and Surawicz[10] identified only 2 cases of endocarditis in association with upper gastrointestinal endoscopy and found the connection between the diagnostic procedure and the development of endocarditis unconvincing in both. It would be difficult to understand why there should be prophylaxis for transesophageal echocardiography but not for upper gastrointestinal endoscopy.

Acknowledgment: We would like to thank Jutta Wagner, MD, and the other colleagues from the Department of Microbiology for their cooperation.

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Prevalence of Cardiac Abnormalities Early in the Course of Systemic Lupus Erythematosus

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Cardiac lesions involving the endocardium, myocardium, pericardium and coronary vessels are well described in patients with systemic lupus erythematosus (SLE) both in clinical and necropsy studies.[1-4] However, all these studies have evaluated patients with long-standing disease (mean duration 3 to 8 years).[1-3] Information on cardiac involvement early in the course of the disease is lacking. We studied 18 unselected consecutive patients recently diagnosed as having SLE for the presence of cardiac abnormalities by echocardiography.

The patient group consisted of 18 subjects with SLE (5 men, 13 women with a mean age of 25 ± 6 years [range 13 to 38]). All fulfilled the revised criteria of the American Rheumatism Association for the diagnosis of SLE.[5] *All patients had clinical activity as judged by an activity score*[6] *(mean activity score 11 ± 5). The mean duration of illness was 8 ± 3 months (range 3 to 12). The control group consisted of 20 healthy subjects (6 men, 14 women with a mean age of 28 ± 6 years). They had no history of heart disease, systemic hypertension or other medical problems. All echocardiographic studies (M-mode, 2-dimensional and pulsed Doppler) were performed with an ATL ultramark 8 imaging system by a single observer. Widely accepted qualitative and quantitative criteria for Doppler evaluation of valvular dysfunction were used.*[7,8] *Diastolic transmitral flow velocities were measured during quiet respiration. Results are expressed as mean ± standard deviation. Data from patients and control subjects were compared by Student's* t *and chi-square tests with correction for continuity. No patient had a history of cardiac symptoms or evidence of valvular heart disease or hypertension on examination. The systolic/diastolic pressure of patients was 124 ± 23/81 ± 11 mm Hg and did not differ from that of the controls (120 ± 12/80 ± 6 mm Hg, p = not significant). Echocardiographic indexes of both systolic and diastolic function were within normal limits (Table I). Pericardial effusion was observed in 2 patients (11%) but in no control subject. No patient had valvular abnormalities such as thickening or vegetations on 2-dimensional echocardiography. Doppler echocardiography did not reveal valvular dysfunction in any patient.*

TABLE I Echocardiographic Findings in Patients with Systemic Lupus Erythematosus and in Control Subjects

Variable	Patients	Control Subjects	p Value
Echocardiographic Dimensions (mm)			
Aorta	19 ± 2	20 ± 6	NS
Left atrium	20 ± 3	21 ± 6	NS
Left ventricle			
End-diastolic	30 ± 3	34 ± 10	NS
End-systolic	19 ± 3	22 ± 6	NS
Ventricular septum	9 ± 2	9 ± 1	NS
Left ventricular posterior wall	8 ± 1	8 ± 1	NS
Indexes of Systolic Function			
LVEF	76 ± 6	77 ± 6	NS
Fractional shortening (%)	38 ± 5	39 ± 6	NS
Vcf (circ/s)	1.5 ± 0.3	1.4 ± 0.3	NS
PEP/LVET	0.3 ± 0.1	0.3 ± 0.1	NS
Indexes of Diastolic Function			
E/A	1.5 ± 0.3	1.6 ± 0.1	NS
EF slope (cm/s^2)	474 ± 139	500 ± 71	NS

Values are expressed as mean ± standard deviation.
A = peak flow velocity during atrial contraction; E = peak flow velocity of left ventricular early diastolic filling; EF slope = deceleration rate of peak early diastolic flow velocity; LVEF = left ventricular ejection fraction; LVET = left ventricular ejection time; NS = not significant; PEP = preejection period; Vcf = velocity of circumferential fiber shortening.

Valvular abnormalities (regurgitation or vegetations) have been described in 18 to 50% of patients with SLE.[1-3] Diastolic dysfunction has also been well documented in SLE.[9] The prevalence of these cardiac abnormalities has been reported to be a function of the dura-

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tion of the disease and the age of the patients.[1,3] Cardiac abnormalities have thus far not been evaluated in patients with SLE at the onset of the disease. In our study, the only abnormality we found was pericardial effusion in 2 of 18 patients. However, the number of patients studied by us is small and these patients were much younger than patients in previous studies.[1,3] These 2 factors may have influenced our results. Despite these limitations, our study indicates that cardiac involvement is rare in SLE in the first year of the disease.

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Focal Myocardial Necrosis Associated with Multiple Sclerosis of the Medulla

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A debate exists as to the capacity of the central nervous system to induce vasospasm of resistance vessels in the coronary circulation both in healthy persons and in patients with coronary artery disease. A view exists suggesting that direct central neural stimulatory effects on the coronary arteries are minimal[1] and that central nervous system stimulation as occurs in head injury results in a generalized autonomic response with circulating catecholamines arising from the adrenal gland causing toxic damage to the myocardium.[2] A contrasting view is that the extensive intrathoracic sympathetic nervous system that directly innervates the coronary arteries when stimulated can induce myocardial ischemia, which, if prolonged, induces myocardial infarction.[3] In this report, we describe a young woman with a brief history of multiple sclerosis involving the medulla who presented with myocardial infarction, and subsequently died.

The 21-year-old patient presented 2 months before her death with recent onset of paresthesia of the right hand and foot, slurred speech and diplopia. A clinical diagnosis of multiple sclerosis was made and she responded to low-dose steroids. Four weeks later she suddenly developed severe headache and right-sided weakness, and presented to the emergency ward in respiratory arrest requiring immediate ventilatory support. Blood pressure was 100/60 mm Hg, heart rate 50 beats/min and spontaneous respiratory rate 8 per min. When fluids were administered she developed pulmonary edema and multiple ventricular ectopy. Electrocardiogram showed Q waves V_{1-3} *with nonspecific ST and T abnormalities. Creatine kinase was marginally elevated to 340 U and white blood count was 30,000. The patient was obtunded and responded poorly to therapy. Echocardiography 12 hours later demonstrated global akinesia with decreased anterolateral and posterolateral wall motion and an ejection fraction of 44%. Serum catecholamines were: noradrenaline 626 pg/ml (normal 258 ± 82) and adrenaline 209 pg/ml (normal <50). A friction rub was heard. Cardiac catheterization 96 hours after admission demonstrated normal coronary arteries and left ventricular function. The patient responded to steroid administration with some improvement in the central nervous system state; she continued to have tachycardia. A tracheostomy was performed as she required respiratory support. After 3 weeks of hospitalization she again developed hypotension and arrhythmia. Her central nervous system status deteriorated and life support systems were withdrawn.*

At necropsy the heart was of normal weight (225 g). The left ventricle was hypercontracted and the myocardium showed a mottled subendocardial pallor. There were minute focal areas of myocardial necrosis and subendocardial hemorrhages that were particularly prominent in the papillary muscles and trabeculae. All major coronary arteries and branches were normal and widely patent. Microscopically, the subendocardial pallor was noted to be mainly due to extensive areas of small to larger confluent foci of acute myocardial necrosis (Figure 1). Small lesions were marked by foci of myocytolysis and contraction bands (Figure 2A). While the predominant lesions were acute, subacute to chronic lesions characterized by slight mononuclear infiltrate and early fibrosis were also present (Figure 2B). There was no evidence

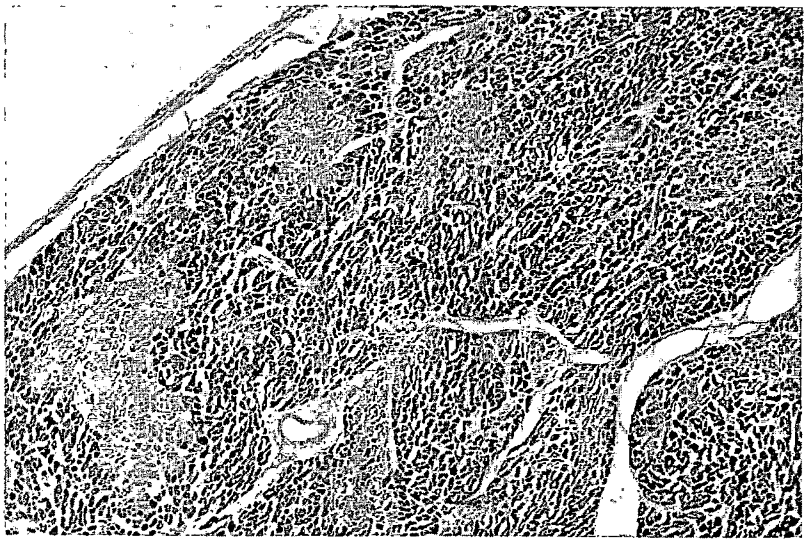
FIGURE 1. Subendocardial myocardium showing extensive areas of acute necrosis (phosphotungstic acid-hematoxylin stain).

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of vasculitis. Interstitial fibrosis was noted and there were some epicardial lesions. Electronmicroscopy showed myofibrillary loss and lipofuscin pigment.

The brain showed extensive subacute demyelinating plaques in the brain stem and, characteristically, a few older periventricular white matter lesions. The most severe lesions were at the caudal end of the fourth ventricle in both upper and lower medulla (Figure 3). These large geographic areas of demyelination involved the nucleus ambiguus and dorsal motor vagal nuclei, bilaterally. The demyelinating nature of the lesions was confirmed by myelin and axonal stains. There were no lesions in the hypothalamus. There was no evidence of a vascular lesion or vasculitis in the central nervous system.

The observation of a large area of demyelinating plaques in the region of the medulla suggests primary involvement of the vasomotor center. Dampney[4] demonstrated that specific vascular beds are represented in the subretrofacial nucleus with connections to the nucleus tractus solitarius, lateral hypothalamus and intermediolateral cell columns. Presumably the destruction of the myelin in the medulla led to excessive sympathetic stimulation of the coronary resistance vessels with sufficient impairment of coronary blood flow that myocardial infarction occurred. That central nervous system stimulation of this magnitude can occur has not been heretofore reported in humans to our knowledge.

Direct neural control of the coronary circulation has been reviewed by Feigl[5] who reported that such stimulation decreases coronary blood flow, whereas myocardial oxygen demand is enhanced. Usually, the toxic effects of synaptically released noradrenaline is blunted by myocardial release of adenosine.[6] In our patient the intensity of stimulation or lack of protective factors was such that myocardial necrosis ensued. It is

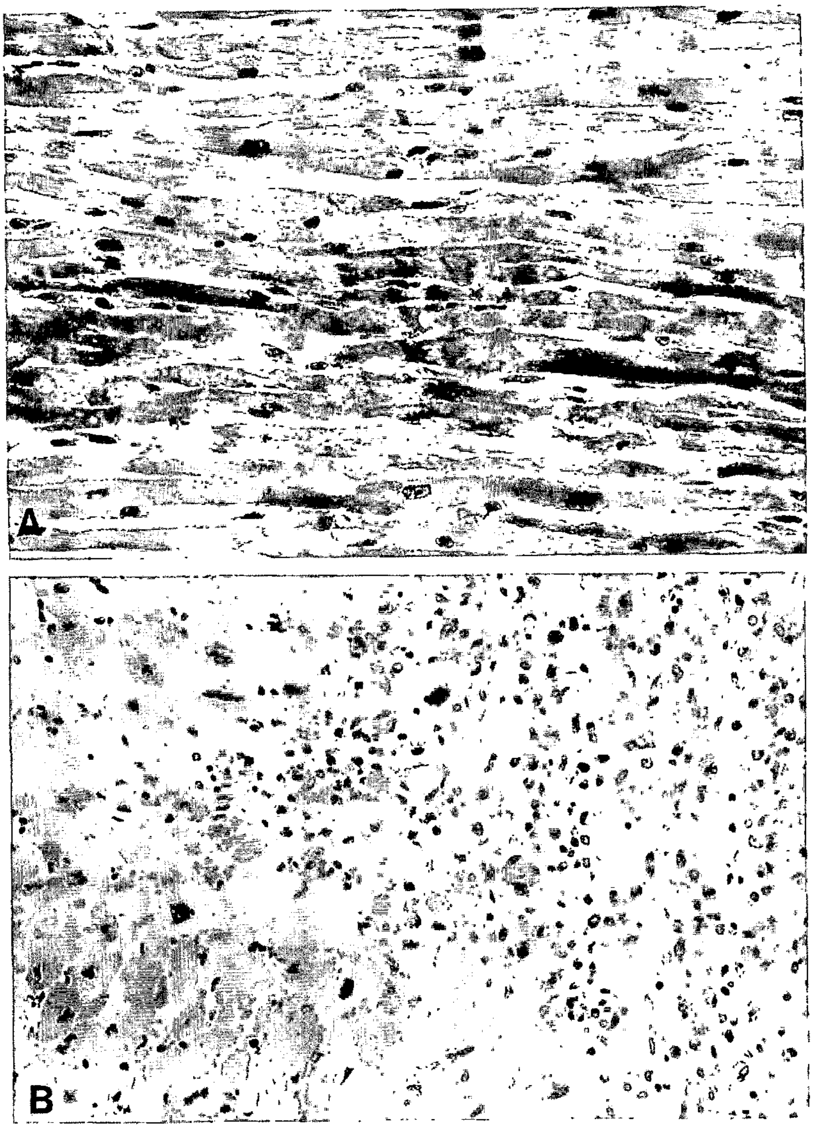

FIGURE 2. ***A,*** **characteristic microscopic foci of acute myocytolysis and contraction bands (Masson trichrome stain).** ***B,*** **foci of subacute necrosis marked by early fibrosis and mononuclear cell infiltrate.**

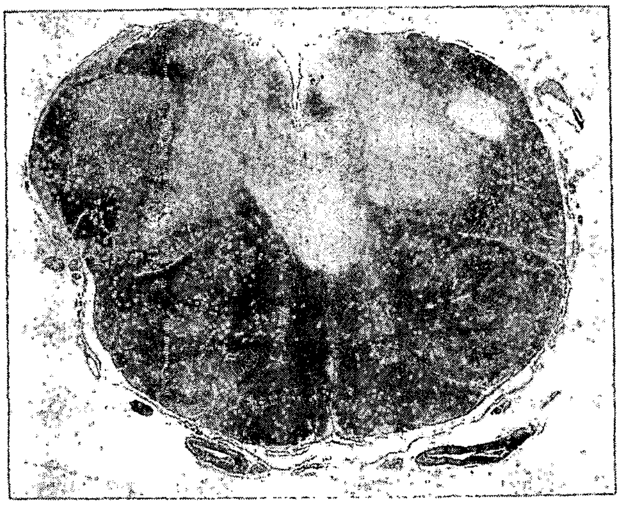

FIGURE 3. Slide mount of the medulla showing large geographic areas of demyelination involving the nucleus ambiguus and dorsal motor nucleus of the vagus, bilaterally.

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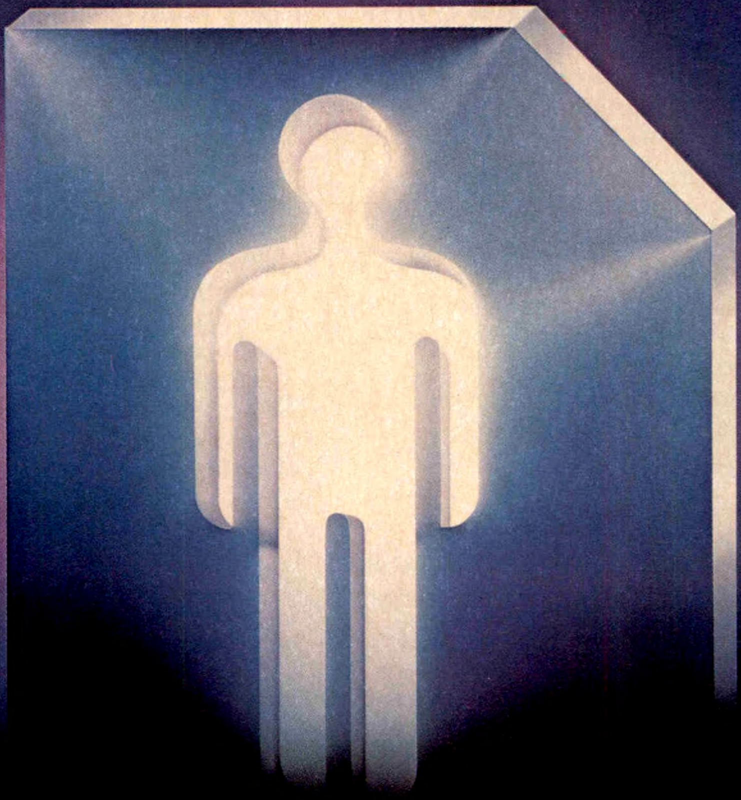

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Early Detection of Acute Myocardial Infarction by Measurement of Mass Concentration of Creatine Kinase-MB

Johannes Mair, Erika Artner-Dworzak, Anton Dienstl, Peter Lechleitner, Bernhard Morass, Jörn Smidt, Ina Wagner, Christof Wettach, and Bernd Puschendorf

Immunoenzymometric measurements of mass concentrations increase the diagnostic sensitivity and performance of creatine kinase (CK)-MB in the diagnosis of acute myocardial infarction (AMI) when compared with measurements of CK-MB activity by immunoinhibition and total CK activity measurements. Pathologic increase occurred significantly earlier in CK-MB mass concentrations than in CK-MB and CK activity, with a median difference of 1 hour each. Before initiating thrombolytic therapy, the sensitivity of CK-MB mass was significantly higher than CK-MB activity during the 0- to 6-hour period and significantly higher than CK activity during the 2- to 4-hour period after the onset of chest pain. Consequently, it is often possible to diagnose an AMI on the basis of increased CK-MB mass concentrations even at a time when CK and CK-MB activities are still within the reference interval.

1551

Increased Risk of Death and Cardiac Arrest from Encainide and Flecainide in Patients After Non-Q-Wave Acute Myocardial Infarction in the Cardiac Arrhythmia Supression Trial

Toshio Akiyama, Yudi Pawitan, Henry Greenberg, Chien-Suu Kuo, Robin A. Reynolds-Haertle, and the CAST Investigators

Whether antiarrhythmic agents exert differential side effects after acute myocardial infarction (AMI) between Q-wave AMI (Q-AMI) and non-Q-wave AMI (non-Q AMI) is unknown. A total of 2,371 patients (70% with Q-AMI, 26% with non-Q AMI, and 4% unknown) entered the titration phase with encainide, flecainide and moricizine of the Cardiac Arrhythmia Suppression Trial. No significant differences existed between Q-AMI and non-Q-AMI patients for death and cardiac arrest rates, suppression rate of ventricular premature complexes, and nonrandomization rate. In all, 1,498 patients entered the follow-up phase with encainide, flecainide, and their matching placebos. Encainide and flecainide significantly elevated death/cardiac arrest rate in both non-Q-AMI (8.7%, p

<0.01) and Q-AMI (7.8%, p = 0.04) patients. However, the relative risk for encainide and flecainide over placebo in the non-Q-AMI patients was 8.7, which was significantly higher than 1.7 for the Q-AMI patients (p = 0.03).

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Comparative Quantitative Angiographic Analysis of Directional Coronary Atherectomy and Balloon Coronary Angioplasty

Victor A. W. M. Umans, Kevin J. Beatt, Benno J. W. M. Rensing, Walter R. M. Hermans, Pim J. de Feyter, and Patrick W. Serruys, with the technical assistance of Eline Montauban van Swijndregt

The immediate and long-term efficacies of coronary atherectomy and balloon angioplasty are compared. Quantitative coronary analysis was selected as a means for objective assessment of procedural results. Two comparable groups of 30 patients who underwent either atherectomy or angioplasty were matched for location of stenosis and reference diameter with identical baseline stenosis characteristics. Directional atherectomy resulted in a twofold increase in mean luminal diameter compared with that of balloon angioplasty (1.53 vs 0.77 mm; p <0.0001). At follow-up, the decrease in minimal luminal gain was more pronounced in the group with atherectomy than in that with angioplasty (0.92 vs 0.35 mm; p <0.0009). These results indicate that in matched groups atherectomy appears more effective than balloon angioplasty based on the immediate result. However, this initial superiority is lost during follow-up. Thus, the final utility of directional atherectomy is equal to balloon angioplasty.

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Clot-Selective Coronary Thrombolysis with Low-Dose Synergistic Combinations of Single-Chain Urokinase-Type Plasminogen Activator and Recombinant Tissue-Type Plasminogen Activator

James M. Kirshenbaum, Raymond D. Bahr, John T. Flaherty, Victor Gurewich, Herbert J. Levine, Joseph Loscalzo, Richard R. Schumacher, Eric J. Topol, Dennis W. Wahr, Eugene Braunwald, and the Pro-Urokinase for Myocardial Infarction Study Group

Simultaneous infusions of low-dose recombinant tissue-type plasminogen activator and single-chain urokinase-type plasminogen activator were investigated in 23 patients treated within 6 hours of symptoms of an acute myocardial infarction. Infarct artery patency at 90 minutes was achieved in 16 patients (70%) after a 1-hour intravenous infusion of 20 mg of t-PA and 16.3 mg of scu-PA. There were only modest effects on circulating coagulation factors. Combination therapy may thus allow substantial reductions in total thrombolytic doses while still achieving effective fibrin-specific coronary thrombolysis.

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Effectiveness of Double Bolus Alteplase in the Treatment of Acute Myocardial Infarction

John A. Purvis, Tom G. Trouton, Michael J. D. Roberts, Pascal McKeown, Michael G. Mulholland, Gavin W. N. Dalzell, Carol M. Wilson, George C. Patterson, Sam W. Webb, Mazhar M. Khan, Norman P. S. Campbell, and A. A. Jennifer Adgey

Fifty-nine consecutive patients presenting within 6 hours of the onset of symptoms of acute myocardial infarction were treated with 150 mg of soluble aspirin orally, and either 70 or 100 mg of alteplase divided into 2 intravenous bolus injections separated by 30 minutes. Dosage regimens were either 20 followed by 50 mg (group A), 50 mg followed by 20 mg (group B), or 50 followed by 50 mg (group C). Coronary arteriography 90 minutes after the first bolus showed patency rates were 15 of 20 (75%) patients in both groups A and B, and 18 of 19 (95%) in group C (overall patency rate 48 of 59 (81%), 95% confidence interval 72 to 91%). Although there was no statistically significant difference in patency between the 3 dosage regimens there was a trend toward increased patency at 90 minutes in group C. No episodes of bradyarrhythmia, hypotension or cerebrovascular bleeding were observed after double bolus therapy. There were 7 episodes (12%) of reocclusion, and 3 deaths (5%) within 1-month follow-up. Double bolus alteplase therapy is a convenient, highly effective and safe method of promoting early coronary artery patency.

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Relation of Technetium-99m Pyrophosphate Accumulation to Time Interval After Onset of Acute Myocardial Infarction as Assessed by a Tomographic Acquisition Technique

Thomas Krause, Wolfgang Kasper, Andreas Zeiher, Carl Schuemichen, and Ernst Moser

Technetium-99m pyrophosphate (Tc-99m PYP) myocardial scintigraphy was performed in 110 clinically stable patients at different times after acute myocardial infarction. From data obtained, it is concluded that a persisting Tc-99m PYP uptake >1 month after acute myocardial infarction is rarely found using the tomographic imaging technique in clinically stable patients with coronary artery disease. Positive Tc-99m PYP tomography is a reliable indicator of acute myocardial necrosis.

1581

Prognostic Significance of Silent Myocardial Ischemia in Variant Angina Pectoris

Raffaele Bugiardini, Alberico Borghi, Biagio Sassone, Andrea Pozzati, and Paolo Puddu

The present study was undertaken to investigate the short-term (1 month) prognostic significance of silent myocardial ischemia in variant angina. Accordingly, 48-hour Holter monitoring and coronary angiography were performed in 54 patients with transient ST elevation admitted to the coronary care unit for worsening of symptoms. Of these patients, 20 had a major coronary event (group 1), and the remaining 34 had a good clinical outcome (group 2). Overall, only 9% of the ischemic episodes were associated with angina. The duration of ischemia per 24 hours (including both ST elevation and depression) was consistently greater in group 1 than in group 2. This was in keeping with the observation of ≥1 long-lasting (≥10 minutes) episode of ST elevation in 18 of the 20 patients in group 1 versus 4 of the 34 in group 2. Most patients in group 1 (16 of 20) had complex coronary stenosis due to plaque rupture, which occurred in only 4 of the 34 patients in group 2. Conversely, coronary artery spasm was frequently observed in both groups of patients. Thus, silent myocardial ischemia is an important predictor of adverse clinical outcome in variant angina. Spasm without plaque disruption has a benign prognosis.

1587

Felodipine (Once Daily) Versus Nifedipine (Four Times Daily) for Prinzmetal's Angina Pectoris

Diego Ardissino, Stefano Savonitto, Antonio Mussini, Paola Zanini, Alberto Rolla, Paolo Barberis, Marco Sardina, and Giuseppe Specchia

In 30 consecutive patients with Prinzmetal's angina pectoris, the antiischemic effect of felodipine administered at doses of 10 and 20 mg once daily was compared with that of nifedipine at a dose of 20 mg 4 times daily. Twenty-four-hour Holter monitoring was performed during a 2-day placebo run-in and at the end of each of 3 consecutive 6-day periods during which the 3 active treatments were administered in randomized sequence. The therapeutic regimens tested proved to be similarly effective; primary end points (ischemic episodes recorded by Holter monitoring, and anginal attacks reported on diary cards) occurred in 5 of 27 (19%) patients during nifedipine treatment, and in 7 (26%) and 3 (11%) during felodipine treatment with 10 and 20 mg, respectively (p = not significant). The distribution of residual ischemic episodes demonstrated that treatment with felodipine once daily provides 24-hour antiischemic protection. It is concluded that for Prinzmetal's angina pectoris, 24-hour antiischemic protection may be achieved with administration of felodipine once daily.

1593

Effects of Daily High-Intensity Exercise on Myocardial Perfusion in Angina Pectoris

Iain C. Todd, Michael S. Bradnam, Michael B.D. Cooke, and David Ballantyne

The effect of daily intensive exercise training on myocardial perfusion in patients with angina pectoris was studied. Planar thallium scintigraphy was used to delineate the ischemic defects before starting exercise training and again at 1 year. A significant reduction in the extent of myocardial ischemia compared with that in control subjects was demonstrated after exercise training. These changes were most marked in the anterolateral and apical regions.

Continued on page A18

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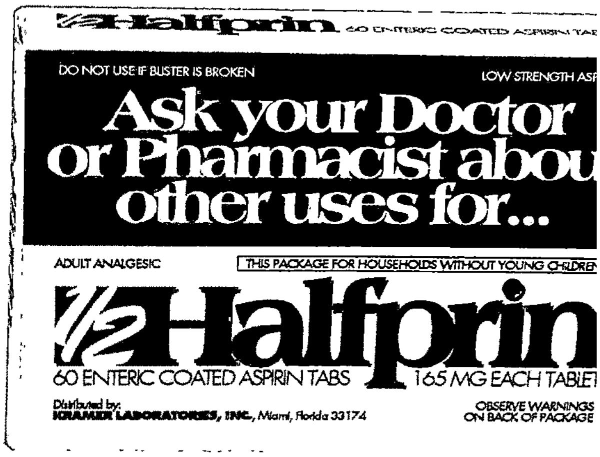
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* REFERENCES

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1600

Silent Versus Symptomatic Ischemia During a Thallium-201 Exercise Test

Mark I. Travin, Angel R. Flores, Charles A. Boucher, John B. Newell, and Paul J. LaRaia

One hundred thirty-four patients with silent ischemia during an exercise test, defined by thallium-201 redistribution, were compared with 134 age-, sex-, and peak heart rate–matched patients who had symptomatic ischemia during the test. Despite equivalent exercise levels, patients with silent ischemia had less frequent and less severe ST-segment depression, a less frequently abnormal blood pressure response to exercise, and less extensive and less severe thallium-201 redistributing defects. Patients with silent ischemia were less likely to undergo elective early revascularization, but the outcome of the 2 groups in terms of adverse cardiac events was otherwise similar. An index combining the extent and severity of thallium-201 redistributing defects best predicted early revascularization in the group with silent ischemia; the percent maximal predicted heart rate for age attained was best predictive in the symptomatic group. For both groups, the occurrence of nonfatal myocardial infarction or cardiac death was best predicted by a thallium-201 image finding.

1609

Experience with Low-Dose Intracoronary Recombinant Tissue-Type Plasminogen Activator for Nonacute Total Occlusions Before Percutaneous Transluminal Coronary Angioplasty

Nicholas A. Ruocco, Jr., Jesse W. Currier, Alice K. Jacobs, Thomas J. Ryan, and David P. Faxon

The ability of low-dose intracoronary recombinant tissue-type plasminogen activator to lyse nonacute occlusive thrombi before angioplasty was tested in 12 patients with total occlusions and in 5 with functional total occlusions. Mean clinical duration of thrombus was 14.8 ± 22 days. There was a significant improvement in severity of stenosis after recombinant tissue-type plasminogen activator by both digital caliper and quantitative videodensitometric area assessment ($p < 0.004$). TIMI flow improved by ≥ 1 grade in 11 patients. This approach warrants further investigation because it has the potential to improve the primary angioplasty success rate in patients with occlusive thrombi.

1614

Comparison of Angiographic Findings and Demographic Variables in Patients with Coronary Artery Disease Presenting with Acute Pulmonary Edema Versus Those Presenting with Chest Pain

Susan P. Graham and George W. Vetrovec

One hundred nineteen patients presenting with pulmonary edema were compared with 119 patients presenting with chest pain. Left main and 3-vessel coronary artery diseases were equally frequent in the 71 patients with pulmonary edema and the 93 with chest pain who underwent catheterization, despite infrequent angina in the first group. More patients with pulmonary edema were black, hypertensive and diabetic, but there were

Continued on page A22

EMINASE®

ANISTREPLASE 30 u

INDICATIONS AND USAGE: EMINASE® ANISTREPLASE, is indicated for use in the management of acute myocardial infarction (AMI) in adults, for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see **CLINICAL PHARMACOLOGY**).

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, EMINASE® is contraindicated in the following situations: ■ active internal bleeding ■ history of cerebrovascular accident ■ recent (within 2 months) intracranial or intraspinal surgery or trauma (see **WARNINGS**) ■ intracranial neoplasm, arteriovenous malformation, or aneurysm ■ known bleeding diathesis ■ severe, uncontrolled hypertension. EMINASE® should not be administered to patients having experienced severe allergic reactions to either this product or Streptokinase.

WARNINGS: Bleeding: (See ADVERSE REACTIONS) The most common complication associated with EMINASE® therapy is bleeding. The types of bleeding associated with thrombolytic therapy can be divided into two broad categories: 1. Internal bleeding involving the gastrointestinal tract, genitourinary tract, retroperitoneal, ocular, or intracranial sites. 2. Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention). The concomitant use of heparin anticoagulation may contribute to the bleeding. Some of the hemorrhagic episodes occurred one or more days after the effects of EMINASE® had dissipated, but while heparin therapy was continuing. As fibrin is lysed during EMINASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites). Intramuscular injections and nonessential handling of the patient should be avoided during treatment with EMINASE®. Venipunctures should be performed carefully and only as required. Should an arterial puncture be necessary following administration of EMINASE®, it is preferable to use an upper-extremity vessel that is accessible to manual compression. A pressure dressing should be applied, and the puncture site should be checked frequently for evidence of bleeding. Each patient being considered for therapy with EMINASE® should be carefully evaluated and anticipated benefits should be weighed against potential risks associated with therapy. In the following conditions, the risks of EMINASE® therapy may be increased and should be weighed against the anticipated benefits: ■ recent (within 10 days) major surgery (e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of non-compressible vessels) ■ cerebrovascular disease ■ recent gastrointestinal or genitourinary bleeding (within 10 days) ■ recent trauma (within 10 days) including cardiopulmonary resuscitation ■ hypertension: systolic BP ≥180 mmHg and/or diastolic BP ≥110 mmHg ■ high likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation) ■ subacute bacterial endocarditis ■ acute pericarditis ■ hemostatic defects including those secondary to severe hepatic or renal disease ■ pregnancy ■ age >75 years (Use of EMINASE® in patients over 75 years old has not been adequately studied.) ■ diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions ■ septic thrombophlebitis or occluded AV cannula at seriously infected site ■ patients currently receiving oral anticoagulants (e.g., warfarin sodium) ■ any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias: Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when injections of EMINASE® are administered.

Hypotension: Hypotension, sometimes severe, not secondary to bleeding or anaphylaxis, has occasionally been observed soon after intravenous EMINASE® administration. Patients should be monitored closely and, should symptomatic or alarming hypotension occur, appropriate symptomatic treatment should be administered.

PRECAUTIONS: General: Standard management of myocardial infarction should be implemented concomitantly with EMINASE® treatment. Invasive procedures should be minimized (see **WARNINGS**). Anaphylactoid reactions have rarely been reported in patients who received EMINASE®. Accordingly, adequate treatment provisions such as epinephrine should be available for immediate use.

Readministration: Because of the increased likelihood of resistance due to antistreptokinase antibody, EMINASE® may not be as effective if administered more than 5 days after prior EMINASE® or Streptokinase therapy or streptococcal infection, particularly between 5 days and 6 months. Increased antistreptokinase antibody levels between 5 days and 6 months after EMINASE® or Streptokinase administration may also increase the risk of allergic reactions. Repeated administration of EMINASE® within one week of the initial dose has occurred in a small number of patients treated for AMI and non-AMI conditions. The incidence of hematomas/bruising was somewhat greater in those patients who received repeat doses of EMINASE® but otherwise the adverse event profile was similar to those who received one dose.

Laboratory Tests: Intravenous administration of EMINASE® will cause marked decreases in plasminogen and fibrinogen and increases in thrombin time (TT), activated partial thromboplastin time (APTT), and prothrombin time (PT). Results of coagulation tests and/or measures of fibrinolytic activity performed during EMINASE® therapy may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. EMINASE®, when present in blood in pharmacologic concentrations, remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (2000 to 3000 KIU/mL) can, to some extent, mitigate this phenomenon.

Drug Interactions: The interaction of EMINASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as aspirin and dipyridamole) may increase the risk of bleeding if administered prior to EMINASE® therapy.

Use of Anticoagulants: EMINASE® alone or in combination with antiplatelet agents and anticoagulants may cause bleeding complications. Therefore, careful monitoring is advised, especially at arterial puncture sites. In clinical studies, a majority of patients treated received anticoagulant therapy postdosing with EMINASE® during their hospital stay and a minority received heparin pretreatment with EMINASE®. The use of antiplatelet agents increased the incidence of bleeding events similarly in patients treated with EMINASE® or nonthrombolytic therapy. There was no evidence of a synergistic effect of combined EMINASE® and antiplatelet agents on bleeding events. In addition, there was no difference in the incidence of hemorrhagic CVA's in EMINASE® treated patients who did or did not receive aspirin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Studies to determine mutagenicity and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested.

Pregnancy (Category C): Animal reproduction studies have not been conducted with EMINASE®. It is also not known whether EMINASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. EMINASE® should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether EMINASE® is excreted in human milk. Because many drugs are excreted in human milk, the physician should decide whether the patient should discontinue nursing or not receive EMINASE®.

Pediatric Use: Safety and effectiveness of EMINASE® in children have not been established.

ADVERSE REACTIONS: Bleeding: The incidence of bleeding (major or minor) varied widely from study to study and may depend on the use of arterial catheterization and other invasive procedures, patient population, and/or concomitant therapy. The overall incidence of bleeding in patients treated with EMINASE® in clinical trials (n=5275) was 14.6%, with nonpuncture-site bleeding occurring in 10.2%, and puncture-site bleeding occurring in 5.7%, of these patients. Bleeding at the puncture site occurred more frequently in clinical trials in which the patients underwent immediate coronary catheterization (13.3%, n=637) compared with those who did not (3.0%, n=2023). The incidence of presumed intracranial bleeding within 7 days postdosing with EMINASE® was 0.57% (n=5275; 0.34% etiology confirmed hemorrhagic; 0.23% etiology not confirmed) compared to 0.16% (n=1249) after nonthrombolytic therapy. In the AIMS trial the overall incidence of bleeding in patients treated with EMINASE® was 14.8% compared with 3.8% for placebo. The incidence of specific bleeding events was:

Type of Bleeding	EMINASE® (n=500)	Placebo (n=501)
Puncture site	4.6%	<1%
Nonpuncture site hematoma	2.8%	<1%
Hematuria/Genitourinary	2.4%	<1%
Hemoptysis	2.2%	<1%
Gastrointestinal hemorrhage	2.0%	1.4%
Intracranial	1.0%	<1%
Gum/Mouth Hemorrhage	1.0%	0
Epistaxis	<1%	<1%
Anemia	<1%	<1%
Eye Hemorrhage	<1%	<1%
Hemorrhage (unspecified)	<1%	0

In this study there was no difference between EMINASE® and placebo in the incidence of major bleeding events. Should serious bleeding (not controlled by local pressure) occur in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial), any concomitant heparin should be terminated immediately and the administration of protamine to reverse heparinization should be considered. If necessary, the bleeding tendency can be reversed with appropriate replacement therapy. Minor bleeding can be anticipated mainly at invaded or disturbed sites. If such bleeding occurs, local measures should be taken to control the bleeding (see **WARNINGS**).

Cardiovascular: The most frequently reported adverse experiences in EMINASE® clinical trials (n=5275) were arrhythmia/conduction disorders which were reported in 38% of patients treated with EMINASE® and 46% of nonthrombolytic control patients. Hypotension occurred in 10.4% of patients treated with EMINASE® compared to 7.9% for patients who received nonthrombolytic treatment (see **WARNINGS**).

Allergic-type Reactions: Anaphylactic and anaphylactoid reactions have been observed rarely (0.2%) in patients treated with EMINASE® and are similar in incidence to Streptokinase (0.1% anaphylactic shock in one study). These included symptoms such as bronchospasm or angioedema. Other milder or delayed effects such as urticaria, itching, flushing, rashes, and eosinophilia have been occasionally observed. A delayed purpuric rash appearing one to two weeks after treatment has been reported in 0.3% of patients. The rash may also be associated with arthralgia, ankle edema, gastrointestinal symptoms, mild hematuria, and mild proteinuria. This syndrome was self-limiting and without long-term sequelae.

Risk of Viral Transmission: Six batches of EMINASE® (five different batches of Lys-Plasminogen) were used in clinical trials designed specifically to monitor possible hepatitis non-A, non-B transmission. No case of hepatitis was diagnosed in patients receiving EMINASE®. Lys-Plasminogen is derived from human plasma obtained from FDA approved sources and tested for absence of viral contamination, including human immunodeficiency virus type-1 (HIV-1) and hepatitis B surface antigen. The manufacturing process includes a vapor-heat treatment step for inactivation of viruses. The entire manufacturing process has also been validated to yield a cumulative reduction of $\geq 10^{2}$ fold HIV-1 infectious particles, i.e., $\geq 10^{6}$ infectious particles removed by vapor-heat treatment and a cumulative total of $\geq 10^{15}$ infectious particles removed by the various steps in the purification process.

Causal Relationship Unknown: Since the following experiences may also be associated with AMI or other therapy, the causal relationship to EMINASE® administration is unknown. The following adverse experiences were infrequently (<10%) reported in clinical trials: **Body as a Whole**—chills, fever, headache, shock; **Cardiovascular**—cardiac rupture, chest pain, emboli; **Dermatology**—purpura, sweating; **Gastrointestinal**—nausea and/or vomiting; **Hemic and Lymphatic**—thrombocytopenia; **Metabolic and Nutritional**—elevated transaminase levels; **Musculoskeletal**—arthralgia; **Nervous**—agitation, dizziness, paresthesia, tremor, vertigo; **Respiratory**—dyspnea, lung edema.

DOSAGE AND ADMINISTRATION: Administer EMINASE® as soon as possible after the onset of symptoms. The recommended dose is 30 units of EMINASE® administered only by intravenous injection over 2 to 5 minutes into an intravenous line or vein.

Reconstitution: 1. Slowly add 5 mL of Sterile Water for Injection, U.S.P., by directing the stream of fluid against the side of the vial. 2. Gently roll the vial, mixing the dry powder and fluid. **Do not shake.** Try to minimize foaming. 3. The reconstituted preparation is a colorless to pale yellow transparent solution. Before administration, the product should be visually inspected for particulate matter and discoloration. 4. Withdraw the entire contents of the vial. 5. The reconstituted solution should not be further diluted before administration or added to any infusion fluids. No other medications should be added to the vial or syringe containing EMINASE®. 6. If EMINASE® is not administered within 30 minutes of reconstitution, it should be discarded.

HOW SUPPLIED: EMINASE® is supplied as a sterile, lyophilized powder in 30-unit vials. NDC 57294-030-20.

Storage: Store lyophilized EMINASE® between 2-8°C (36-46°F). Do not use beyond the expiration date printed on the vial.

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no differences in the results of cardiac catheterization between black and white patients.

1619

Significance of Signal-Averaged P-Wave Changes During Exercise in Patients with Coronary Artery Disease and Correlation with Angiographic Findings

Michael M. Myrianthefs, Myrvin H. Ellestad, Ronald H. Startt-Selvester, and Randy Crump

The maximal P-wave duration was measured in signal-averaged, time-aligned leads, on a 12 simultaneous lead electrocardiogram during recovery of an exercise stress test. The study group consisted of 75 patients with angiographically documented stenosis ≥50% in at least 1 major coronary artery, and a control group of 47 with no or minimal coronary atherosclerosis and normal left ventriculogram. There was a statistically significant ($p < 0.001$) increase in P-wave duration throughout recovery in the group with coronary artery disease when compared with control subjects. The increase in P-wave duration ≥20 ms was used as an additional parameter to the standard criteria for the test interpretation. Sensitivity increased from 57 to 75%, with a small decrease in specificity (85 to 77%). It is concluded that measurement of the P-wave duration in recovery adds diagnostic power for detection of ischemia during exercise.

1625

Assessment of Medial Thinning in Atherosclerosis by Intravascular Ultrasound

Elma J. Gussenhoven, Peter A.V. Frietman, Salem H.K. The, Robert J. van Suylen, Frans C. van Egmond, Charles T. Lancée, Hero van Urk, Jos R.T.C. Roelandt, Theo Stijnen, and Nicolaas Bom

Intravascular ultrasound was used to examine the inverse relation between media and lesion thicknesses. In vitro (40 MHz), the images of 39 muscular arteries were compared with the corresponding histologic section. The median media thickness was 0.8 mm in the absence of a lesion, decreasing to 0.3 mm in the area of maximal atherosclerosis. The ultrasound data correlated closely with histologic measurements (0.6 and 0.3 mm, respectively). In vivo study was performed in peripheral arteries of 29 patients. The median media thickness was 0.6 mm in the absence of a lesion, decreasing to 0.1 mm in the area with maximal atherosclerosis. This study revealed for the first time that in vitro data that show the inverse relation between media and lesion thicknesses can be translated to humans.

1633

Coronary Hemodynamics and Coronary Flow Reserve After Intracoronary Diltiazem in Humans

Matty C. Vrolix, Dimitris Sionis, Jan H. Piessens, Johan Van Lierde, Jos L. Willems, and Hilaire De Geest

Epicardial coronary artery diameter, coronary blood flow, and coronary blood flow velocity were assessed at baseline and after a 0.5 mg intracoronary bolus of diltiazem in nonstenotic coronary arteries of awake humans. Patients were randomized to pretreatment with either placebo or isosorbide dinitrate; coronary flow reserve was measured before and after ad-

Continued on page A25

ministration of diltiazem. Diltiazem resulted in significant increases in epicardial diameter and blood flow. Coronary flow reserve decreased significantly due to both an increase in baseline blood flow and a decrease in papaverine-induced hyperemic flow. The increases in coronary diameter and blood flow after diltiazem were comparable whether patients were pretreated with placebo or nitrates. However, the decrease in flow reserve was restricted to patients pretreated with placebo. A diltiazem-induced decrease in coronary flow reserve could represent yet another mechanism of action of this drug.

1638

Regional Myocardial Perfusion and Metabolism Assessed by Positron Emission Tomography in Children with Kawasaki Disease and Significance of Abnormal Q Waves and Their Disappearance

Muneo Yoshibayashi, Nagara Tamaki, Kenya Nishioka, Masahiko Matsumura, Tadashi Ueda, Shinji Temma, Yoshiharu Yonekura, Keiji Yamashita, Junji Konishi, and Haruki Mikawa

To clarify the significance of abnormal Q waves and their disappearance in patients with Kawasaki disease, regional myocardial perfusion and metabolism were assessed by positron emission tomography (PET) with ^{13}N-ammonia and ^{18}F-fluorodeoxyglucose, and wall motion by left ventriculography in 14 patients. Almost all regions with abnormal Q waves showed abnormal PET findings. PET demonstrated evidence of metabolic activity in 57% of regions with persistent and in 67% of those with transient abnormal Q waves. There was no significant difference in wall motion between regions with persistent and transient abnormal Q waves. Persistence of abnormal Q waves on serial electrocardiograms was significantly shorter in metabolically active than in inactive regions. In conclusion, abnormal Q waves are reliable clues to the presence of ischemic myocardial injury. Disappearance of abnormal Q waves does not necessarily mean normalization of regional perfusion, metabolism or function. Their early disappearance may imply metabolically active myocardial regions.

1646

Usefulness of the Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio in Predicting Angiographic Coronary Artery Disease in Women

Mun K. Hong, Philip A. Romm, Kathleen Reagan, Curtis E. Green, and Charles E. Rackley

The relation between lipids and angiographic coronary artery disease (CAD) in women was investigated in 108 consecutive women undergoing diagnostic coronary angiography (group I) and in 56 women with total cholesterol <200 mg/dl (group II). On multivariate analysis, total/high-density lipoprotein (HDL) cholesterol ratio was the independent variable most predictive of the presence of CAD, defined as ≥25% narrowing in a major coronary artery, in both groups. The ratio was also the best correlate of the extent (number of narrowed arteries) and severity (percent maximum stenosis) of CAD in group I, and severity in group II. Neither total cholesterol nor triglyceride levels correlated with the presence of CAD in both groups. Thus, among women undergoing diagnostic coro-

nary angiography, total/HDL cholesterol ratio is the best predictor of CAD regardless of the total cholesterol level and should be determined in all women being screened for CAD risk.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1651

Radiofrequency Catheter Ablation of Accessory Pathways: A Learning Experience

Richard A. Leather, James W. Leitch, George J. Klein, Gerard M. Guiraudon, Raymond Yee, and You Ho Kim

Radiofrequency catheter ablation of accessory pathways was attempted in an initial series of 75 patients (84 pathways) with the Wolff-Parkinson-White syndrome. A conservative approach was used attempting to limit fluoroscopy time to 1 hour. Overall success rate of 71% (60 of 84) included a success rate of 52% for accessory pathways in the first 3 months of the series (n = 23), 60% for the second 3 months (n = 23) and 90% for the last 3 months (n = 38). Mean fluoroscopy time of 33 ± 21 minutes for successful procedures differed from that for unsuccessful ones of 63 ± 24 minutes ($p = 0.001$). There were no major complications. A conservative approach limiting fluoroscopy time to 1 hour for most patients is safe and yields success rates approaching 90% after a learning experience. This supports the suggestion that ablation may be first-line therapy for patients with Wolff-Parkinson-White syndrome.

1656

Reduction in Medical Care Cost Associated with Radiofrequency Catheter Ablation of Accessory Pathways

Michael de Buitleir, Joao Sousa, Steven F. Bolling, Rafel El-Atassi, Hugh Calkins, Jonathan J. Langberg, William H. Kou, and Fred Morady

The cost of definitive therapy was compared in 25 patients who underwent radiofrequency catheter ablation of accessory pathways in 1990 and 25 patients who underwent surgical ablation of accessory pathways in 1989. All patients had a single accessory pathway except for 2 patients in the radiofrequency group and 5 patients in the surgical group each of whom had 2 accessory pathways. The success rate of the procedure was 96% in each group. Mean duration of hospitalization was 3 ± 1 days in the radiofrequency group and 9 ± 4 days in the surgical group ($p < 0.0001$). The total cost of therapy was $14,919 ± $6,740 in the radiofrequency group compared with $53,265 ± $12,755 in the surgical group ($p < 0.0001$). Radiofrequency catheter ablation of accessory pathways results in a dramatic reduction in the cost of definitive therapy in patients with the Wolff-Parkinson-White syndrome.

Continued on page A28

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1662

Comparative Cost-Effectiveness Analysis of Quinidine, Procainamide and Mexiletine

Philip J. Podrid, Peter R. Kowey, William H. Frishman, Renée J. Goldberg Arnold, Diana J. Kaniecki, J. Robert Beck, and Joni R. Beshansky

Quinidine and procainamide have the potential for major organ toxicity, whereas mexiletine has been reported to have little risk of organ toxicity, serious proarrhythmia or congestive heart failure, but a relatively high incidence of nuisance side effects. In light of the potential adverse effects of all antiarrhythmic agents as highlighted by the Cardiac Arrhythmia Suppression Trial, the relative cost-effectiveness of quinidine, mexiletine and procainamide in patients with symptomatic or malignant ventricular arrhythmias, or both, was assessed. Based on a review of >1,000 published reports, studies included in the analysis examined ≥1 of these agents in adults with adequate efficacy or safety data, or both. Thirty-seven separate side effects were included in the analysis. Data were analyzed using a decision analysis/cost-effectiveness model. In terms of overall cost, 12 months of mexiletine would engender $875, quinidine $1,239 and procainamide $1,911 of expenses, suggesting that mexiletine is a cost-effective alternative therapy for ventricular arrhythmias.

CONGESTIVE HEART FAILURE

1668

Reproducibility and Relation to Mean Heart Rate of Heart Rate Variability in Normal Subjects and in Patients with Congestive Heart Failure Secondary to Coronary Artery Disease

Diederik Van Hoogenhuyze, Norman Weinstein, Gary J. Martin, Jerry S. Weiss, John W. Schaad, X. Nader Sahyouni, Dan Fintel, Willem J. Remme, and Donald H. Singer

To assess reproducibility of heart rate (HR) variability and relation to HR, HR variability was determined in 2 successive 24-hour ambulatory electrocardiograms from 33 normal subjects and 22 patients with congestive heart failure using 3 methods: (1) standard deviation of all mean 5-minute normal sinus RR intervals over 24 hours; (2) mean of the standard deviation of all normal sinus RR intervals during successive 5-minute periods over 24 hours (SD), and (3) coefficient of variation of the SD, a new measure, that compensates for HR changes. Mean HR was significantly higher and HR variability lower in patients with CHF than in normal subjects, but considerable overlap occurred. Mean group values for HR and HR variability were highly reproducible in both groups (day-to-day correlations ranging from 0.87 to 0.97). However, sometimes considerable day-to-day variation occurred in individual patients with CHF and in normal subjects (46 and 51%, respectively), especially those with high HR variability. Low HR variability showed less variation. Mean HR correlates with HR variability ($r = 0.49$ to $r = 0.63$). HR must therefore be considered in interpreting HR variability changes. The coefficient of variation measure minimizes this problem.

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VALVULAR HEART DISEASE

1677

Comparison of Transthoracic and Transesophageal Echocardiography for Assessment of Left-Sided Valvular Regurgitation

Ramon Castello, Leonard Fagan, Jr., Patricia Lenzen, Anthony C. Pearson, and Arthur J. Labovitz

To compare transthoracic and transesophageal echocardiography in the evaluation of left-sided valvular regurgitation, 18 patients who underwent both transesophageal and transthoracic echocardiographic studies with no change in their clinical status were included in this study. Total agreement regarding presence or absence of aortic regurgitation and its severity was found in 88 patients (75%). Total agreement in mitral regurgitation grade was found in only 74 patients (63%). Differences between transthoracic and transesophageal echocardiography in aortic regurgitation evaluation appear not to be clinically important. In mitral regurgitation, significant differences exist between these 2 techniques, with transesophageal echocardiography being much more sensitive. These differences are greatest in the presence of prosthetic mitral valves.

CONGENITAL HEART DISEASE

1681

Pulmonary Valve-Moderator Band Distance and Association with Development of Double-Chambered Right Ventricle

Pierre C. Wong, Stephen P. Sanders, Richard A. Jonas, Steven D. Colan, Ira A. Parness, Tal Geva, Richard Van Praagh, and Philip J. Spevak

The distance between the pulmonary valve anulus and the moderator band was measured to quantify the displacement of the moderator band in double-chambered right ventricle (DCRV). This measurement was obtained from the initial echocardiograms of 8 infants with a ventricular septal defect (VSD) who eventually developed DCRV, and from those of 2 age-matched control groups (10 patients with no structural heart disease, and 10 with a VSD who did not develop DCRV). The moderator band was already significantly displaced toward the pulmonary valve in the initial studies of the 8 patients who developed DCRV. The distance between the pulmonary valve to the moderator band is easily measured from the echocardiogram and appears to identify patients with a VSD at risk to develop DCRV.

MISCELLANEOUS

1687

Acute and Long-Term Effects of Nifedipine on Pulmonary and Systemic Hemodynamics in Patients with Pulmonary Hypertension Associated with Diffuse Systemic Sclerosis, the CREST Syndrome and Mixed Connective Tissue Disease

Martin A. Alpert, Thomas A. Pressly, Vaskar Mukerji, Charles R. Lambert, Basanti Mukerji, Hercules Panayiotou, and Gordon C. Sharp

To assess the effect of nifedipine on pulmonary and systemic hemodynamics in patients with pulmonary hypertension and diffuse systemic sclerosis, the CREST syndrome and mixed connective tissue disease, cardiac catheterization was performed just before and after incremental doses of oral nifedipine (acute study, n = 10) and 3 to 6 months later with oral nifedipine therapy (long-term study, n = 6). Nifedipine produced a significant decrease in mean pulmonary vascular resistance in both the acute and long-term study. The results indicate that oral nifedipine may be effective in treating pulmonary hypertension associated with diffuse systemic sclerosis, the CREST syndrome and mixed connective tissue disease.

1692

Echocardiographic Assessment of Left Ventricular Function and Wall Motion at High Altitude in Normal Subjects

Kazuo Hirata, Toshihiko Ban, Yousuke Jinnouchi, and Shigeru Kubo

The first precise studies of left ventricular (LV) function at an altitude of over 5,000 m by 2-dimensional echocardiography were performed. The subjects were 11 climbing members (aged 21 to 43 years) of the Kyoto University Medical Research Expedition of Xixabangma (8,027 m) in 1990. Examinations were performed at sea level, at the base camp (5,020 m), and twice at the advanced base camp (5,650 m). At high altitude, heart rate increased to 136% of the sea level value, but gradually decreased in the degree of increment after acclimatization. LV end-diastolic volume decreased significantly by 70%. In the early stage at high altitude, mean rate of circumferential fiber shortening, ejection fraction and % fractional shortening were significantly augmented and showed little change during the long-term stay. Regional wall motion at high altitude (measured by the centerline method) decreased at the septal wall due to hypoxic pulmonary hypertension. However, LV posterolateral wall motion showed a compensatory increase.

1698

Coronary Adrenergic Hyperreactivity in Patients with Syndrome X and Abnormal Electrocardiogram at Rest

Piero Montorsi, Franco Fabbiocchi, Alessandro Loaldi, Luca Annoni, Alvise Polese, Nicoletta de Cesare, and Maurizio D. Guazzi

Changes in coronary blood flow (thermodilution) and epicardial arterial diameter (quantitative angiography) in response to adrenergic stimulation with cold pressor test (before and after propranolol) were investigated in patients with syndrome X with normal electrocardiogram at rest (group 1:

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17 patients), and negative T waves in the anterior leads (group 2: 22 patients). The systemic hemodynamic response to cold pressor test was similar in both groups. Group 1 had vasodilatation of both micro- (coronary flow increase and resistance decrease) and macrocirculation (diameter increase of the distal coronary segment), whereas group 2 had opposite changes. After propranolol, group 1 had a similar vasomotor response to cold stimulus, whereas the vasoconstrictor response of group 2 appeared to be tempered by the drug. Thus, patients with syndrome X and negative T waves in electrocardiogram at rest had a coronary vasoconstrictor response of the small epicardial arteries and arterioles to adrenergic influences; propranolol is not detrimental, but may even be beneficial.

1704

Gender Differences in Left Ventricular Anatomy, Blood Viscosity and Volume Regulatory Hormones in Normal Adults

Giovanni de Simone, Richard B. Devereux, Mary J. Roman, Antonello Ganau, Shu Chien, Michael H. Alderman, Steven A. Atlas, and John H. Laragh

Correlates of gender differences in blood viscosity and left ventricular (LV) anatomy were studied in 110 normotensive adults. LV wall thicknesses and mass were positively related to blood viscosity, because of higher values in both variables in men. LV chamber size was inversely related to blood viscosity, especially among women. Aging increased the gender difference in blood viscosity, associated with increased LV chamber size and fractional shortening in women and a diminished gender difference in LV mass. With increasing age, atrial natriuretic factor increased and plasma renin activity decreased in women ($p < 0.001$ and $p < 0.02$), but not in men. Thus gender differences in LV anatomy and blood viscosity are interrelated; with aging, normal women exhibit LV and hormonal changes compatible with volume expansion, which may contribute to the known increase in LV mass and loss of cardioprotection.

1709

Cost-Effectiveness Analysis of the Use of Digoxin Immune Fab(Ovine) for Treatment of Digoxin Toxicity

Josephine A. Mauskopf and Thomas L. Wenger

Each year many patients have digitalis toxicity severe enough to require extensive hospital treatment. Digoxin immune Fab(ovine)–Fab fragments have been shown to reverse digitalis toxicity and substantially reduce the risk of death. We derive estimates of the difference in clinical outcomes and medical care costs when treating with this new drug. Treatment with Fab fragments is generally associated with an increase in total medical care costs for seriously toxic patients because more of them survive the toxic episode and require additional medical care before discharge from the hospital. For these patients, the estimated cost per life-year saved is between $1,900 and $5,400. When Fab fragments are used to treat less seriously toxic patients, total medical care costs decrease because of an estimated decreased number of days in the coronary care unit and decreased use of pacemakers and other aggressive treatments.

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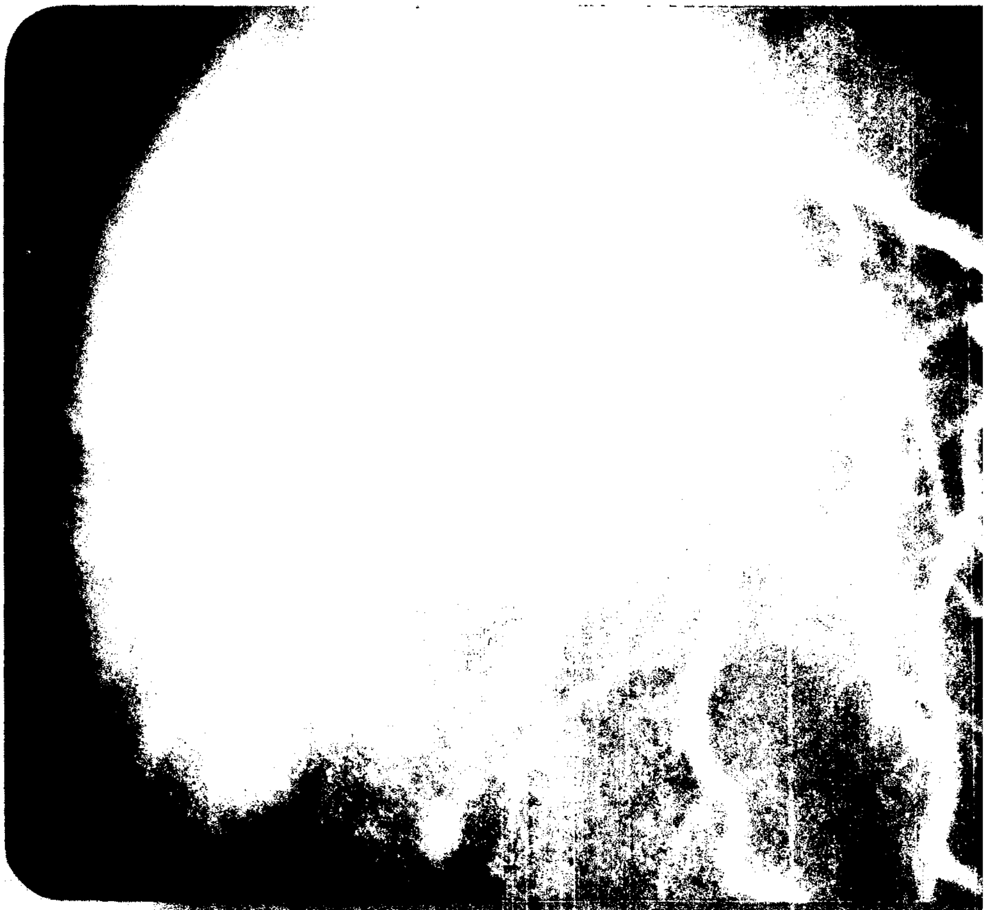

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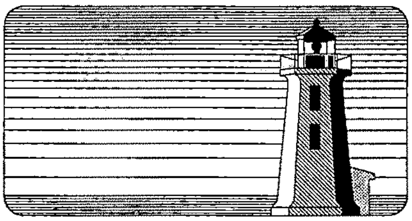

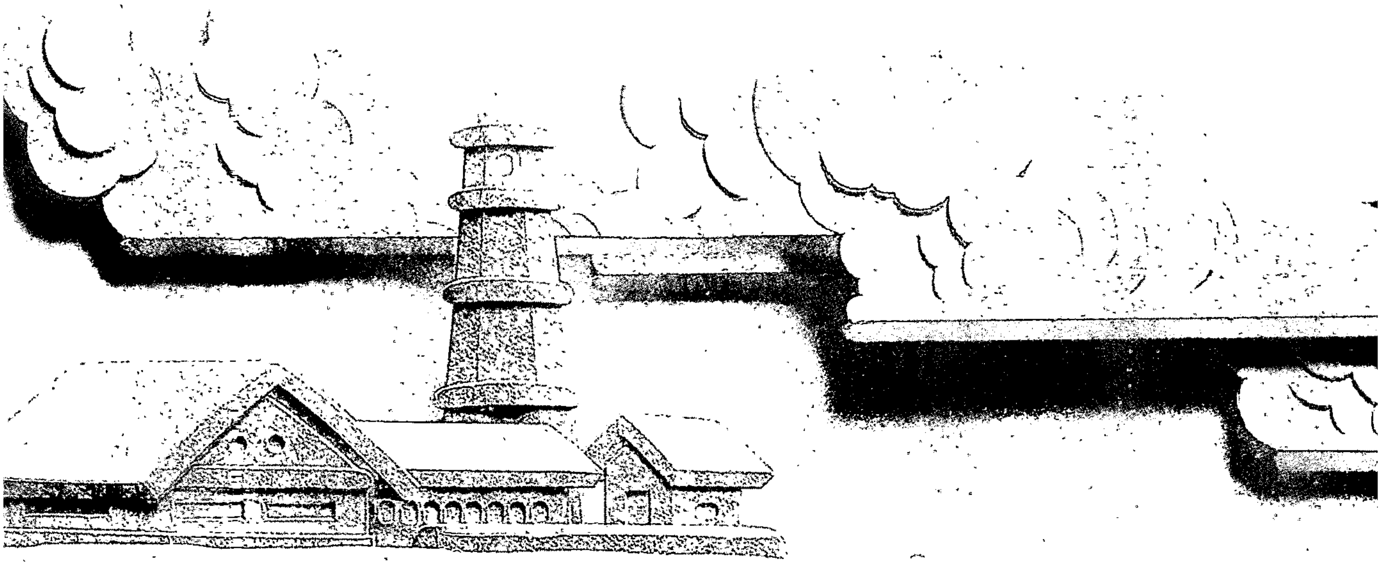

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CORONARY ARTERY DISEASE

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Early Detection of Acute Myocardial Infarction by Measurement of Mass Concentration of Creatine Kinase-MB

Johannes Mair, MD, Erika Artner-Dworzak, MD, Anton Dienstl, MD, Peter Lechleitner, MD, Bernhard Morass, Jörn Smidt, Ina Wagner, Christof Wettach, and Bernd Puschendorf, MD

The diagnostic sensitivity and performance of immunoenzymometric measurements of creatine kinase (CK)-MB mass concentrations in the early diagnosis of acute myocardial infarction (AMI) were examined and compared with the sensitivities and performances of CK and CK-MB activity, in the context of simultaneous measurements of CK, CK-MB activity, and CK-MB mass concentrations in serially drawn blood samples obtained immediately from 36 patients with AMI and 126 patients with chest pain on admission to the emergency room of the department of internal medicine. In the 36 patients with AMI, who were all admitted no later than 4 hours after the onset of chest pain, pathologic increase occurred significantly earlier in CK-MB mass than in both CK and CK-MB activity, with a median difference of 1 hour each. In patients coming to the emergency room (51 with AMI, 51 with angina pectoris and 24 with chest pain not related to coronary artery disease), CK-MB mass was the best diagnostic measurement for AMI of all markers tested (significantly higher efficiency, Youden index and likelihood ratio than both CK and CK-MB activity). Before initiating thrombolytic therapy, the sensitivity of CK-MB mass is significantly higher than CK-MB activity during the 0- to 6-hour period and significantly higher than CK activity during the 2- to 4-hour period after the onset of chest pain. Consequently, it is often possible to diagnose an AMI on the basis of increased CK-MB mass concentrations even at a time when CK and CK-MB activities are still within the reference interval.

(Am J Cardiol 1991;68:1545–1550)

The diagnosis of an acute myocardial infarction (AMI) has traditionally been based on the triad of characteristic chest pain, specific electrocardiographic abnormalities and increased serum concentrations of cardiac enzymes, especially creatine kinase (CK) isoenzyme-MB. Thrombolytic therapy requires an early detection of a suspected AMI, because the success rate of recanalization decreases proportionally to the time elapsed between attack and treatment.[1] In addition, rapid and reliable diagnosis will be increasingly important for correct triage of patients into various hospital areas for the appropriate degree of care. However, because the differential diagnostic value of chest pain is limited[2] and the electrocardiographic changes have varying degrees of sensitivity[3-5] and specificity,[6,7] measurement of serum enzymes as a reflection of myocardial cell damage plays an important role in the diagnosis of an AMI in patients with a nondiagnostic electrocardiogram. At present, immunoinhibition assays for CK-MB activity are widely used in emergency laboratories because they are easy to handle, ideally suited for automation and provide results rapidly.[8] The presence of atypical CK forms and adenylate kinase activities in serum may lead to false-positive results. Moreover, CK-MB activity in serum does not increase until the fourth to eighth hour after the onset of chest pain,[9] and therefore lacks the desirable degree of sensitivity during the early stages of AMI. Instead of quantifying enzyme activity, recently introduced 2-site immunoenzymometric assay measures the CK-MB isoenzyme concentration itself by one antibody binding to its M-subunit and

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the other binding to its B-subunit.[10,11] Most of these highly specific immunoassays for CK-MB can be used for rapid determinations. The purpose of the present study was to determine whether improvements in analytic sensitivity by measurements of CK-MB mass concentration will produce a diagnostically more sensitive marker with improved diagnostic performance for the early detection of AMI.

METHODS

Patients: The study was performed in 2 parts.

PART 1: The object of the first part of our study was to identify existing differences in the time courses of CK-MB mass, CK and CK-MB activity in plasma after AMI. Thirty-six patients (23 men and 13 women) ranging in age from 40 to 83 years (median 61) presented to the hospital's coronary care unit within 4 hours (range 0.5 to 4, median 2 hours) after the onset of symptoms and gave informed consent for extra blood samples to be drawn. All patients subsequently proved to have sustained an AMI (32 Q-wave and 4 non-Q-wave myocardial infarctions, and 16 anterior and 20 inferior wall infarctions). Myocardial infarction was diagnosed by a cardiologist according to World Health Organisation criteria[12] without having recourse to CK-MB mass results. Eighteen patients received intravenous streptokinase (1.5 million U in 60 minutes), 1 patient intravenous urokinase (2 million U in 10 to 15 minutes), 15 patients were given intravenous recombinant tissue-type plasminogen activator after a bolus of 10 and 50 mg initially during the first hour and 20 mg each during the second and third hours after admission. Two patients did not receive thrombolytic treatment because of contraindications. All patients additionally received routine coronary care and were treated with intravenous heparin, acetylsalicyclic acid, nitrates, occasionally β blockers and antiarrhythmic drugs as needed. Peripheral venous blood samples were collected from an indwelling forearm catheter before starting therapy in the coronary care unit, hourly for the first 10 hours, then at 12, 16, 20, 24, 32, 40 and 48 hours after admission, and daily until the seventh day. Patient care requirements occasionally prevented the taking of a sample.

According to recent findings,[13] coronary angiography was performed only selectively, usually several days after admission. This means that the occurrence of reperfusion in Q-wave infarction could not be documented directly by coronary angiography but had to be inferred from less definitive noninvasive indicators, such as the combined analysis of CK and CK-MB activity release kinetics. Reperfusion of the infarct-related artery in Q-wave infarction results in a more rapid increase in CK and CK-MB and in early peaks of both proteins.[14,15] Early reperfusion was assumed to have occurred if there was both a CK-MB activity peak within 14 hours and a CK peak within 16 hours after the onset of chest pain.[16] According to these criteria, 22 of 30 patients with Q-wave infarction and thrombolytic therapy were classified as "reperfused early."

PART 2: The second part of the study evaluated the diagnostic performance of CK-MB mass concentration measurements for the early, diagnosis of AMI in patients in the emergency room (department of internal medicine) complaining of chest pain as their major symptom. The study population of 126 patients therefore did not include cases of chest contusion or trauma. Fifty-one patients subsequently proved to have sustained an AMI (according to criteria mentioned, median delay from the onset of chest pain to admission, 2.25 hours; range 0.5 to 14.5). Twenty-six patients sustained a Q-wave (median delay; 1.75 hours; interquartile range 1 to 3.5) and 25 a non-Q-wave myocardial infarction (median delay; 4 hours; interquartile range 1 to 7.15). Fifty-one patients presented with angina pectoris. A further 24 patients had chest pain not related to coronary artery disease (3 cases of supraventricular tachycardia, 4 pneumonia with pleurisy, 1 obstructive pulmonary disease, 4 musculoskeletal disorders, 3 pericarditis, 6 pulmonary embolism, 2 esophagitis and 1 case of hypertensive crisis). In these patients a single blood sample was drawn immediately after admission. All patients received routine emergency treatment. All patients with AMI were transferred to the coronary care unit before initiating thrombolytic therapy. None of these patients had received thrombolytic therapy before admission to the hospital.

Laboratory analysis: BLOOD COLLECTION: Blood was collected in ethylenediaminetetraacetate coated tubes. CK and CK-MB activities were assayed without delay. Blood samples for the measurement of CK-MB mass concentrations were centrifuged immediately and the plasma subsequently frozen and stored at -20°C until determination.

CK and CK-MB activity: CK and CK-MB activities were measured by means of an N-acetylcysteine-activated, optimized ultraviolet test from Merck (Darmstadt, Federal Republic of Germany). CK-MB activities were determined by immunoinhibition, based on the presence of CK M-subunit antibodies. The upper limits of the reference interval of CK are 70 U/liter for women and 80 U/liter for men; the normal range of CK-MB activity is $\leq$10 U/liter. CK-MB activities of >10 U/liter and >6% of an increased CK total activity were assumed to indicate myocardial muscle cell damage.

CK-MB mass concentration: CK-MB mass was measured by a microparticle enzyme immunoassay (Abbott, Abbott Park, Illinois) for use with the Abbott IMX™ automated analyzer.[17] This assay has been described in detail elsewhere.[10] The analyzer can process a single specimen in 34 minutes and 24 specimens in 37 minutes. The reference interval (≤7 μg/liter) was established in plasma specimens of 100 apparently healthy blood donors (no history of cardiovascular diseases; 41 men and 59 women; age 19 to 65 years, median 44).

Data analysis: Median, interquartile range and percentiles were calculated to describe continuous variables. The association between continuous variables was analyzed by the Spearman rank correlation test. The Wilcoxon signed-rank and chi-square tests (or Fisher's exact test where appropriate) were used for between-group comparison. Bonferroni adjustment of the p value for multiple comparison was used for between-group comparison of >2 groups. Confidence intervals were calculated according to Gardner and Altman.[18] A p value <0.05 was considered significant. Sensitivity, specificity, efficiency, positive predictive value, negative predictive value, likelihood ratio and Youden index (sensitivity + specificity − 1) were calculated to describe the performance of CK-MB mass concentrations, CK and CK-MB activity in the diagnosis of AMI in emergency room patients.[19-21] Receiver-operating characteristic curves were constructed to discriminate between AMI and no AMI in these patients.

RESULTS

Comparison of time courses of CK-MB mass, CK-MB activity and CK activity in acute myocardial infarction: Criteria describing the release kinetics of CK-MB mass concentrations, CK and CK-MB activity in part 1 AMI patients are listed in Table I. Pathologic increase occurred significantly earlier in CK-MB mass than in CK-MB activity ($p = 0.0001$) and CK activity ($p = 0.0033$). The median difference between the first appearances of CK-MB mass and activity was 1 hour (95% confidence interval, 1 to 2 hours), the median difference between CK-MB mass and CK activity was 1 hour (95% confidence interval, 0 to 2 hours). The sensitivity over time of CK, CK-MB activity and mass concentrations in these patients is shown in Figure 1. The median peak values of all tested markers occurred early after admission owing to the high percentage (73%) of patients with Q-wave AMI with early reperfusion. There was no significant difference in the time to peak values of CK-MB mass and activity. The time courses of CK-MB mass concentration after AMI contrasted more strongly with the normal range than CK and CK-MB activities measured in the same patients. Although the magnitudes of increase (calculated as peak value divided by cutoff value) of CK-MB mass compared with CK-MB activity ($r = 0.93$, $p < 0.0001$) and CK-MB mass compared with CK activity ($r = 0.84$, $p < 0.0001$) correlated well, there was a much higher ($p = 0.0001$) increase in CK-MB mass than in both of the other markers (see Table I). The correlation

TABLE I Release kinetics of CK, CK-MB Activity and CK-MB Mass Concentration in 36 Patients with Acute Myocardial Infarction

	CK-MB Mass	CK-MB Activity	CK Activity
Cutoff value	7 μg/liter	10 U/liter	70 U/liter
Time to first increased plasma values (hours)	3.75 (3–4)	5 (4–6)	4.75 (3.5–5.25)
Time to peak (hours)	12 (10.5–14.25)	12.25 (11–14.25)	13 (11.5–15.75)
Return to normal (hours)	74 (50–80)	53 (36–76)	74 (50–96)
Period of increased plasma values (hours)	69 (33–72)	50 (45–90)	68 (46–78)
Magnitude of increase	32.9 (21.6–69.3)	4.5 (3.9–7.7)	7 (4.3–12)

First appearance in blood, time to peak values and time of return to normal are calculated for the onset of symptoms. Data given are median and 95% confidence interval of the median (in parentheses). The magnitude of increase was calculated by dividing peak values by cutoff values. Thirty patients with Q-wave AMI received intravenous thrombolytic treatment, which resulted in early reperfusion n 22.
CK = creatine kinase.

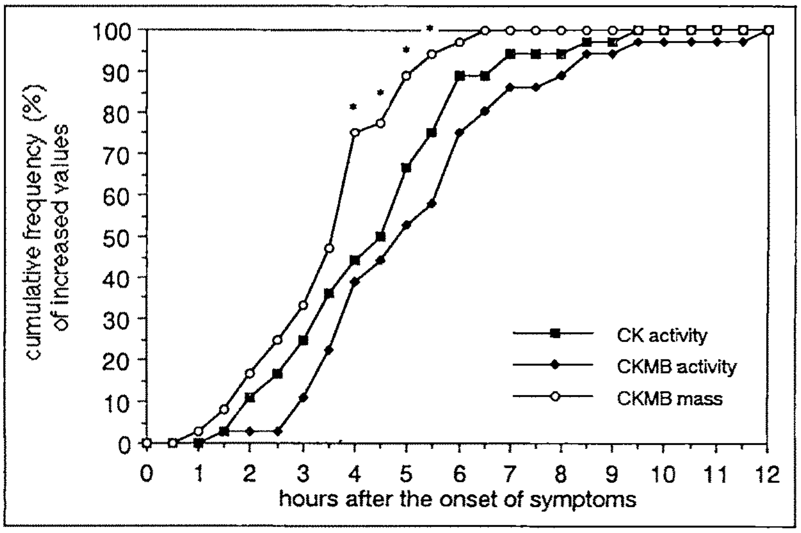

FIGURE 1. Diagnostic sensitivity of creatine kinase (CK)-MB mass, CK-MB and CK activity during the first hours after the onset of symptoms (patients receiving thrombolytic treatment included). The figure is based on the time courses of 36 patients with acute myocardial infarction (AMI) (32 Q-wave, 4 non-Q-wave AMI) presenting within 4 hours after the onset of symptoms. Thirty patients with Q-wave AMI received intravenous thrombolytic treatment, which resulted in early reperfusion in 22. The lowest value of each interval was included in the calculation of the cumulative frequency of increased values. *Asterisks* indicate significant (p <0.05) difference from both CK and CK-MB activity at a given time.

TABLE II Distribution of CK-MB Mass, CK and CK-MB Activity in Emergency Room Patients Investigated

Diagnosis	CK-MB Mass (µg/liter)	CK-MB Activity (U/liter)	CK Activity (U/liter)
Acute myocardial infarction	11.7 (5.3–31.7)	7 (4–12)	68 (47–142)
Angina pectoris	2.7 (2.1–4.1)	4 (4–6)	37 (26–68)
Chest pain, no CAD	2.4 (1.2–5.2)	4 (4–5)	33 (15–59)

Data given are median and interquartile range (in parentheses).
CAD = coronary artery disease; CK = creatine kinase.

found in patients with AMI between maximal CK-MB mass concentrations and maximal CK activity values was 0.84 ($p < 0.0001$), and between maximal CK-MB mass and activity, 0.93 ($p < 0.0001$). The period with increased plasma concentrations of CK-MB mass after AMI, which allowed a diagnosis based on increased biochemical markers, was significantly ($p = 0.0031$) longer than that of CK-MB activity (Table I). The correlation coefficients between CK-MB mass and activity time courses in individual patients ranged from 0.72 to 0.98 (median 0.91).

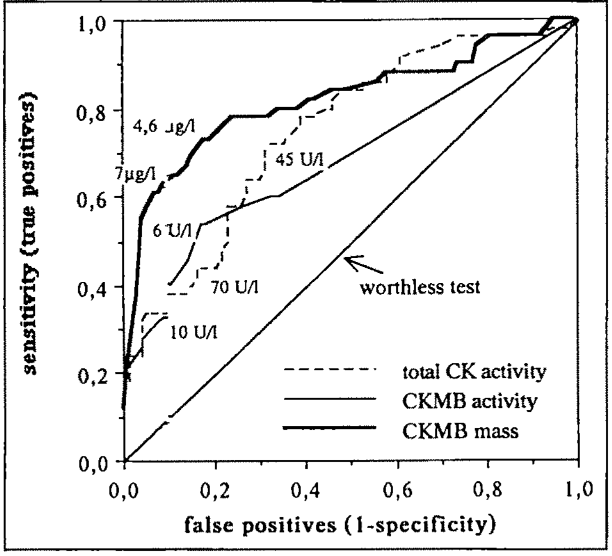

FIGURE 2. Receiver-operating characteristic curves for the discrimination between acute myocardial infarction (AMI) and no AMI and in emergency room patients with chest pain. Curves based on 126 emergency room patients (department of internal medicine). The prevalence of AMI was 0.4. The equation sensitivity of 1−specificity is represented as a *straight diagonal line* and indicates a worthless test. The larger the deviation from this line (and the larger the area under the receiver-operating characteristic curve) the better the discriminative power of the test under scrutiny.

TABLE III Comparison of CK, CK-MB Activity and CK-MB Mass Concentrations for Diagnosing Acute Myocardial Infarction in Patients with Chest Pain on Admission to the Emergency Room

	CK-MB Mass	CK-MB Activity	Total CK Activity
Cutoff value	7 µg/liter	10 U/liter	70 U/liter
Sensitivity	0.57 (0.48–0.66)	0.32 (0.24–0.4)	0.44 (0.35–0.53)
Specificity	0.95 (0.91–0.99)	0.92 (0.87–0.97)	0.82 (0.75–0.89)
Positive predictive value	0.88 (0.82–0.93)	0.72 (0.53–0.91)	0.63 (0.53–0.71)
Negative predictive value	0.76 (0.69–0.83)	0.66 (0.58–0.74)	0.68 (0.6–0.76)
Efficiency	0.79 (0.72–0.86)	0.67 (0.59–0.75)	0.67 (0.59–0.75)
Youden index	0.52 (0.43–0.61)	0.24 (0.17–0.31)	0.26 (0.18–0.34)
Likelihood ratio	11.4 (5.5–17.3)	4 (1.6–6.4)	2.5 (1.8–3.2)

Data are based on 126 emergency room patients (department of internal medicine). The prevalence of acute myocardial infarction was 0.4 (pretest odds 0.68). Ninety-five percent confidence intervals are given in parentheses.
CK = creatine kinase.

Diagnostic performance of CK-MB mass and activity and CK activity to detect acute myocardial infarction in emergency room patients with chest pain: The prevalence of AMI was 0.4 (pretest odds 0.68). Table II lists the distribution of CK-MB mass, CK and CK-MB activity in the emergency room patients studied. The receiver-operating characteristic curves (Figure 2) prove the higher discriminative power of CK-MB mass concentration. The CK-MB mass cutoff value, 7 µg/liter, established in healthy blood donors yields a desirable sensitivity (0.57) and specificity (0.95). Various indicators describing the performance of a diagnostic test are listed in Table III. The sensitivity, positive predictive value, efficiency, Youden index and likelihood ratio of CK-MB mass concentrations were significantly ($p < 0.05$) higher than those of both CK and CK-MB activity. The CK-MB mass assay produced false-positive results in 6 patients, of whom 1 had severe congestive heart failure (14.9 µg/liter), 1 had myocarditis (20.9 µg/liter), 1 had hypertensive crisis (8.2 µg/liter), 1 had cardiomyopathy with direct-current countershock therapy because of ventricular fibrillation (73.2 µg/liter) and 3 had severe angina at rest (8.1, 9.1 and 7.3 µg/liter). CK-MB activities measured in the same blood samples were within the normal range in all but 1 patient (direct-current countershock therapy: 13 U/liter). Subgroup analysis of the sensitivities of CK-MB mass, CK and CK-MB activity in the diagnosis of non-Q-wave AMI yields sensitivities of 0.68 (CK-MB mass), 0.24 (CK-MB activity) and 0.54 (total CK activity). The difference between CK-MB mass and activity (mean 0.43, 95% confidence interval 0.19 to 0.67) was significant ($p = 0.003$), whereas there was no significant difference between CK-MB mass and CK activity sensitivities (mean 0.14, 95% confidence interval −0.11 to 0.39).

Comparison of CK-MB mass, CK and CK-MB activity sensitivities before initiating thrombolytic therapy: Sensitivities of CK-MB mass, CK and CK-MB activity during the early stages of AMI before initiating thrombolytic treatment are listed in Table IV. This table is based on the combined analysis of the data of the emergency room patients investigated and on those blood samples of part 1 AMI patients that were obtained on admission to the coronary care unit before thrombolytic treatment. Patients after cardiopulmonary resuscitation or direct-current countershock therapy were also excluded from data analysis. CK-MB mass was significantly ($p < 0.05$) more sensitive than CK-MB activity for the first 6 hours and significantly ($p = 0.005$) more sensitive than CK activity from the second to the fourth hour after the onset of chest pain.

TABLE IV Comparison of Sensitivity of CK-MB Mass, CK and CK-MB Activity in Early Stages of Myocardial Infarction Before Thrombolytic Treatment

Delay Onset of Symptoms to Blood Sampling	CK-MB Mass	CK-MB Activity	Total CK Activity
≤2 hours	0.25 (0.12–0.38)	0.05 (0.0–0.12)	0.13 (0.02–0.23)
>2 and ≤4 hours	0.71 (0.55–0.87)	0.23 (0.08–0.38)	0.32 (0.16–0.48)
>4 and ≤6 hours	1.0 (0.76–1.0)	0.33 (0.14–0.61)	0.83 (0.55–0.95)

Calculated sensitivities are based on cutoff values 7 μg/liter (CK-MB mass), 10 U/liter (CK-MB activity) and 70 U/liter (CK activity). Ninety-five percent confidence intervals are given in parentheses. Blood samples obtained from patients after cardiopulmonary resuscitation, direct-current countershock or thrombolytic therapy were excluded from data analysis.

CK = creatine-kinase.

DISCUSSION

Published reports contain contradictory accounts of the relation between the mass concentration of CK isoenzyme-MB and its activity. Al-Sheik et al[22] and Dods[23] found evidence suggesting that CK-MB mass is diagnostically more sensitive, whereas other investigators[24–26] report no significant difference. On the basis of more extended and frequent sampling than was undertaken in previous research, the present study demonstrates a statistically significant and clinically relevant difference in the first appearances of CK-MB mass and CK or CK-MB activity in blood after AMI and thrombolytic therapy. Reperfusion could be expected to alter the release kinetics of CK and CK isoenzymes by the washout of enzyme released from injured myocytes. However, the goal must be to diagnose AMI before initiating thrombolytic therapy. Therefore, we tested the sensitivity of CK-MB mass concentrations, CK and CK-MB activities in blood samples obtained before thrombolytic therapy. CK-MB mass was significantly more sensitive than CK-MB activity for the first 6 hours and significantly more sensitive than CK activity from the second to the fourth hour after the onset of chest pain. There was no significant difference in the time to peak values of CK-MB mass and activity, which was consistent with the findings of other investigators.[25,26] The same patients were tested for all 3 biochemical markers, which cancelled possible biases distorting the results (i.e., delay between attack and treatment, different therapies, size and site of infarction, etc.).

The second part of the study tested the clinical relevance to the emergency physician of increased sensitivity of CK-MB mass concentration during evolving myocardial infarction. Of all 3 markers tested, CK-MB mass was most likely to detect AMI in emergency room patients with chest pain. CK-MB mass is superior to CK-MB activity also in the more difficult diagnosis of non-Q-wave AMI. Although maximal Youden indexes (0.39, 0.36 and 0.55) were found at cutoff values of 43 U/liter (CK), 6 U/liter (CKMB) and 4.6 μg/liter, the CK and CK-MB activity cutoff values recommended by the assay's manufacturer and a CK-MB mass cutoff value of 7.0 μg/liter should be used to reduce the rate of false-positive results. The specificities of CK-MB and CK will contrast more strongly in a population including patients with skeletal muscle injury, such as trauma, burns and surgery. Four patients (2 with severe angina at rest, 1 in hypertensive crisis, 1 with severe congestive heart failure) had moderately increased CK-MB mass concentrations, whereas CK-MB activities measured in the same patients were within the normal range. These 4 patients were not diagnosed as having sustained an AMI by the clinician and were classified as "false-positive," causing a decrease in the specificity of CK-MB mass. Whether slightly increased CK-MB mass values in these patients reflect microinfarcts or disseminated heart muscle cell damage missed by electrocardiography and CK-MB activity remains to be elucidated.

Thrombolytic therapy for AMI requires an accurate early marker. CK and CK-MB assays do not reliably diagnose AMI for the first 2 hours after the onset of chest pain. The sensitivity of CK-MB mass concentrations, on the other hand, is sufficiently high during the 2- to 6-hour period and makes possible the diagnosis of an AMI even at a time when CK and CK-MB activities are still within the reference interval. Rapid determination of CK-MB mass is already commercially available. Because some tests — including the one used in the present study — are totally automated and take approximately 30 minutes, they are ideally suited for use in an emergency laboratory. Although the definitive diagnosis of an AMI requires serial CK-MB measurements to detect a characteristic increase and decrease, CK-MB mass concentrations are a valuable diagnostic aid to the emergency physician, especially in patients with chest pain whose electrocardiogram is nondiagnostic.

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Increased Risk of Death and Cardiac Arrest from Encainide and Flecainide in Patients After Non-Q-Wave Acute Myocardial Infarction in the Cardiac Arrhythmia Suppression Trial

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This report examines whether in the Cardiac Arrhythmia Suppression Trial death and cardiac arrest from encainide, flecainide and moricizine during the titration phase and from encainide and flecainide during the follow-up phase were related to presence (Q-wave acute myocardial infarction [Q-AMI]) or absence (non-Q-AMI) of pathologic Q waves. In all, 2,371 patients (70% with Q-AMI, 26% with non-Q-AMI, and 4% unknown) entered the titration phase, starting 117 ± 163 days after index AMI and lasting for an average of 21 days. For the titration phase, no significant differences existed between Q-AMI and non-Q-AMI patients for death and cardiac arrest rate, ventricular premature complex suppression rate, and nonrandomization rate. A total of 1,498 patients entered the follow-up phase of an average of 10 months (starting 129 ± 158 days after the index AMI), and were randomized to encainide or flecainide, or their matching placebos. In the placebo group, non-Q-AMI patients had a significantly lower rate of death and cardiac arrest than Q-AMI patients (1.0 and 4.6%, respectively; $p = 0.04$). Encainide and flecainide significantly elevated death and cardiac arrest rate in both non-Q-AMI patients (8.7%, $p < 0.01$) and Q-AMI patients (7.8%, $p = 0.04$). The relative risk for encainide or flecainide over placebo in the non-Q-AMI patients was 8.7, which was significantly higher than 1.7 observed for the Q-AMI patients ($p = 0.03$). None of the baseline characteristics had any significant interaction with encainide or flecainide.

In conclusion, during the relatively early post-AMI period, therapy with encainide, flecainide or moricizine resulted in similar rates of ventricular premature complex suppression and death/cardiac arrest between non-Q-AMI and Q-AMI groups. In contrast, during the late postmyocardial infarction period, therapy with encainide or flecainide was associated with a much steeper increase in death/cardiac arrest rate in the non-Q-AMI group than in the Q-AMI group.

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In-hospital cardiac mortality is reported to be higher in patients after Q-wave (Q-AMI) than after non-Q-wave acute myocardial infarction (non-Q AMI),[1-4] whereas posthospitalization cardiac mortality and morbidity may be as high or even higher in patients after non-Q-AMI than after Q-AMI.[2,4-8] Furthermore, recurrent myocardial infarction during the first few weeks after AMI appears to be more frequent after non-Q-AMI than after Q-AMI.[4,5] Also, patients after non-Q-AMI appear to have more sudden cardiac deaths after hospital discharge than patients after Q-AMI.[9-11] There have been no studies showing differential effects of antiarrhythmic drugs between Q-AMI and non-Q-AMI patients. The Cardiac Arrhythmia Suppression Trial (CAST) was designed to test the hypothesis that pharmacologic suppression of asymptomatic or mildly symptomatic frequent ventricular premature complexes in the postmyocardial infarction period would reduce sudden cardiac death.[12,13] As reported, patients assigned to encainide and flecainide had a significantly higher cardiac mortality than patients assigned to placebo.[14] In this report, we examine whether mortality during the titration phase and the follow-up period from encainide and flecainide is related to presence or absence of pathologic Q waves.

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*Refer to Reference 14 for list of CAST investigators.

METHODS

Study design: The design of the CAST has been published previously.[14] Patients were enrolled into the titration phase of the study after satisfying the following major criteria: a documented myocardial infarction, ventricular premature complexes ≥6/hour on the 24-hour ambulatory electrocardiographic recording performed between 6 days and 2 years after the qualifying myocardial infarction, a left ventricular ejection fraction ≤0.55 for those enrolled within 90 days of the qualifying myocardial infarction, and ≤0.40 for those enrolled between 90 days and 2 years after the qualifying myocardial infarction. Patients were excluded from the study if they had severely symptomatic or incapacitating ventricular arrhythmias or ≥15 consecutive ventricular premature complexes at a rate of ≥120 beats/min. Each patient gave informed consent. Patients were randomized to the titration sequence encainide-moricizine-flecainide or flecainide-moricizine-encainide when left ventricular ejection fraction was ≥0.30, or encainide-moricizine or moricizine-encainide when left ventricular ejection fraction was <0.30. Two doses were available for each drug: encainide 35 or 50 mg 3 times daily, flecainide 100 or 150 mg twice daily, moricizine 200 or 250 mg 3 times daily. Patients whose ventricular premature complexes were suppressed ≥80% without intolerant side effects during the titration phase were randomized to blinded therapy and were followed at the CAST clinics at 4-month intervals.

Characterization of myocardial infarction using the CAST electrocardiographic code: A standard 12-lead electrocardiogram recorded after qualifying myocardial infarction was interpreted and coded using the CAST electrocardiographic code (see later for definitions) by the site investigator. In this code, electrocardiographic waveform abnormalities are grouped into 4 categories (Q wave, ST-segment elevation, ST-segment depression and T-wave inversion) for 4 anatomic locations (anterior, lateral, inferior and posterior). For each waveform, an age assessment of new, old or indeterminate is made.

Patient selection: For the titration phase, 2,371 patients entered the study between June 15, 1987 and April 19, 1989. We excluded 66 patients because of left bundle branch block and 5 because of paced rhythm. Twenty-four patients had missing data on Q-wave abnormality. This study reports the results on the remaining 2,276 patients, 1,653 with Q-AMI and 623 with non-Q-AMI.

For the follow-up phase, 1,498 patients were suppressed with CAST drugs and were randomized into the main study. A total of 25 and 5 patients were excluded from further analyses because of the presence of left bundle branch block and paced rhythm, respectively. Thirteen patients were excluded for missing data for Q-wave abnormality. Our statistical analysis was restricted to the remaining 1,455 patients, 1,048 patients with Q-AMI and 407 with non-Q-AMI.

Definitions: The locations were: anterior = leads V_1 to V_4; lateral = leads I, aVL, V_5, V_6; inferior = leads II, III, aVF; and posterior = leads V_1, V_2.

Abnormal Q waves are defined as 1 of the following: (1) Any Q wave ≥0.03 second in ≥2 contiguous leads excluding V_1 and aVR (contiguous leads are V_2 to V_6, I and aVL, and II, III and aVF); (2) >50% reduction in the R wave in each of ≥2 contiguous precordial leads compared with a previous electrocardiogram or, in the absence of right bundle branch block or right ventricular hypertrophy, the R-wave amplitude in V_5 or V_6 is <25% of that in V_3 or V_4; (3) R/S ratio of 1 or greater in V_1 or V_2 in the absence of right bundle branch block or right ventricular hypertrophy.

Abnormal ST elevation is defined as any upward convex ST elevation ≥0.1 mV measured 0.08 second after the J point, except for V_1 or V_2; in V_1 or V_2, the ST-segment elevation must be ≥0.2 mV.

Abnormal ST depression is defined as any ST depression ≥0.1 mV measured 0.08 second after the J point.

Abnormal T-wave inversion is defined as any symmetrical T-wave inversion ≥0.1 mV in any of the leads except for aVR when the R-wave amplitude is ≥0.5 mV.

Statistical analyses: Baseline characteristics (between Q-AMI and non-Q-AMI groups) are compared using the standard chi-square tests or *t* tests for categorical or continuous variables, respectively. For survival analysis the exposure time began at the time of randomization to blinded therapy. The patients, who were alive on April 18, 1989, the time the encainide and flecainide study was closed, were censored then. The difference in the relative risks of the active therapy over placebo in different groups is analyzed by including an interaction term between the treatment and the group indicators in the Cox regression model. An adjustment for possible contribution from other variables to the interaction between the non-Q-AMI and active therapy is made by including the interaction terms between the treatment and all possible confounders. These confounders include ST elevation, ST depression, T inversion, age >65 years, ejection fraction ≤30, diuretic use, history of hypertension, congestive heart failure, angina and AMI, and heart rate >74 beats/min. Because not all variables are actually confounders, this method is conservative in the sense that it tends to yield a higher p value for the interaction of interest.

For new or worsened congestive heart failure and nonfatal AMI, only the first event during follow-up is

TABLE I Death and Cardiac Arrest During Titration Phase (drugs: encainide, flecainide or moricizine)

	Alive	D/CA		Total
Q-wave AMI	97.3% (1,608)	2.7% (45)	*	100% (1,653)
Non-Q-wave AMI	97.6% (608)	2.4% (15)		100% (623)

*p = 0.81.
AMI = acute myocardial infarction; D/CA = death and cardiac arrest.

TABLE II Baseline Characteristics for Patients Entering the Follow-Up Phase

Variable	Q-Wave AMI	Non-Q-Wave AMI	p Value
No. of patients	1,048	407	
Age (years)	60.2 ± 9.7	62.7 ± 9.5	*
Ejection fraction	39.2 ± 9.7	41.1 ± 8.9	*
Men (%)	84.4	77.6	*
Before index myocardial infarction, history of			
Hypertension (%)	28.9	35.1	†
Congestive heart failure (%)	11.5	14.0	
Angina (%)	46.0	44.0	
Myocardial infarction (%)	37.4	31.7	†
Concurrent drugs at baseline			
β blocker (%)	32.8	29.0	
Calcium antagonist (%)	49.5	54.5	
Digitalis	19.0	22.1	
Diuretics	29.0	35.4	†
Baseline systolic BP (mm Hg)	124.5 ± 18	127.9 ± 20	*

*p ≤0.01; †p ≤0.05 (expressed as mean ± standard deviation).
AMI = acute myocardial infarction; BP = blood pressure.

TABLE III Baseline Electrocardiographic Characteristics for Patient Entering Follow-Up Phase

Variable	Q-Wave AMI	Non-Q-Wave AMI	p Value
Baseline ECG			
Q waves (%)	100.0	0	
New anterior	24.7	—	
New lateral (%)	6.7	—	
New inferior (%)	25.0	—	
Posterior (%)	10.2	—	
ST elevation	55.9	31.9	*
ST depression (%)	32.1	45.2	*
T inversion (%)	69.7	60.4	*
Heart rate (beats/min)	76.0 ± 15.7	76.0 ± 17.5	
Qualifying Holter			
VPCs/hour	127 ± 260	137 ± 257	
VPCs/hour			
≤10 (%)	15.6	16.7	
10.1–50 (%)	41.4	37.3	
50.1–100 (%)	16.6	16.5	
>100 (%)	26.4	29.5	
Ventricular tachycardia runs/day			
None (%)	78.5	78.4	
1 (%)	11.5	10.8	
2–5 (%)	5.6	6.4	
≥6 (%)	4.3	4.4	

*p ≤0.01.
AMI = acute myocardial infarction; ECG = electrocardiogram; VPCs = ventricular premature complexes.

TABLE IV Relative Risk of Death and Cardiac Arrest from Encainide/Flecainide in Patients with Q-Wave and Non-Q-Wave Myocardial Infarction During Follow-Up

	Death and Cardiac Arrest Rate			
Risk	Placebo	Encainide and Flecainide	Relative	
Q-wave AMI	4.6% (24/520)	7.8% (41/528)	1.7*	‡
Non-Q-wave AMI	1.0% (2/199)	8.7% (18/208)	8.7†	

*p = 0.04; †p <0.01; ‡p = 0.03.
AMI = acute myocardial infarction.

analyzed. Fatal AMI is defined as in the study by Echt et al.[16] The exposure time for a patient who had an event started at the time of randomization to blinded therapy and ended at the time of an event; otherwise it was censored at the time of death/cardiac arrest, withdrawal from the study, or on April 18, 1989.

RESULTS

Titration phase: A total of 2,371 patients were entered into the study between June 15, 1987, and April 18, 1989. The baseline characteristics and survival of these patients are described by Epstein et al.[15] The titration phase lasted for an average of 20 days, with its first titration day occurring 117 ± 163 days after the index AMI. Of the 2,276 patients who entered titration and had complete Q-wave information, 1,653 (73%) had Q-AMI and 623 (27%) had non-Q-AMI. There is no significant difference between the Q-AMI and non-Q-AMI groups in ventricular premature complex suppression (75.8 vs 75.1%, respectively) or nonrandomization rates (18.8 vs 18.0%, respectively). Sixty-three of the 2,371 patients (2.7%) died or had cardiac arrests during titration (60 among the 2,276 patients, Table I), of which 49 were arrhythmic, 12 were cardiac nonarrhythmic, and 2 were noncardiac. There is no significant difference in the death rates between Q-AMI and non-Q-AMI groups (p = 0.81).

Follow-up phase: The 1,498 patients who were randomized to encainide, flecainide, or their matching placebo 129 ± 158 days (mean ± standard deviation) after the index AMI were followed for an average of 10 months. Baseline characteristics of 1,458 patients who had Q-wave data are listed in Table II. Among baseline electrocardiographic characteristics, the non-Q-AMI patients were more likely to have ST depression but were less likely to have T-wave inversion and ST elevation (Table III).

Relative risks of death and cardiac arrest during follow-up phase from encainide and flecainide in Q-AMI and non-Q-AMI groups are listed in Table IV. In the placebo group, non-Q-AMI patients had a significantly lower death rate than Q-AMI patients. The rate of death and/or cardiac arrest in both the non-Q-AMI and Q-AMI groups was significantly greater in the group assigned to encainide or flecainide therapy than to placebo. The non-Q-AMI versus Q-AMI difference observed within the placebo groups, however, disappeared in the groups treated with encainide or flecainide. There was a greater increase in the death and cardiac arrest rate in non-Q-AMI than Q-AMI patients. The relative risk for encainide or flecainide over placebo in the non-Q-AMI group was >5 times higher than for the Q-AMI group.

Using the Cox regression models, possible contributions of other baseline variables to the increased mortality from encainide and flecainide in the non-Q-AMI patients were examined. The adjusted ratio of the encainide/flecainide to placebo relative risk in non-Q-AMI patients to that in Q-AMI patients was 4.55 ($p = 0.07$). None of the baseline variables, including ejection fraction, age and congestive heart failure had any significant interaction with encainide/flecainide. Similar results are found when we excluded patients with right bundle branch block ($p = 0.05$ and 0.10 for the unadjusted and adjusted analyses, respectively).

No statistically significant difference in the rate of congestive heart failure existed between non-Q-AMI and Q-AMI patients in the placebo group or in the treatment group. However, the relative risk of 2.1 for encainide/flecainide compared with placebo among non-Q-AMI patients was marginally higher than the relative risk of 1.0 among Q-AMI patients ($p = 0.11$). Nonfatal myocardial infarction occurred relatively infrequently (46 of 1,455 = 3.2%) in the entire group during the follow-up. Though statistically not significant, the placebo reinfarction rate in non-Q AMI was nearly twice that for Q-AMI in our study (6.0 vs 3.5%). For the treatment group, reinfarction rate in Q-AMI patients was similar to that for the placebo, but the rate for non-Q-AMI patients was one-fourth of that for the placebo (1.4 vs 6.0%).

DISCUSSION

Our study shows that during the early posthospitalization phase after AMI, non-Q-AMI and Q-AMI patients did not differ in the death and cardiac arrest rates or in the ventricular premature complex suppression rates with 3 antiarrhythmic agents. However, during the subsequent 10-month follow-up period, placebo non-Q-AMI patients had a much lower death and cardiac arrest rate than the placebo Q-AMI patients. What was most striking for the treatment groups was the large increase in non-Q-AMI mortality compared with the modest increase in Q-AMI mortality (Table IV). The relative risks differ by a factor of 5. Thus, in the postmyocardial infarction patients enrolled in the CAST, encainide and flecainide appear to have exerted differential adverse effects with respect to time after myocardial infarction and also to presence or absence of Q wave.

Possible explanation of our results: Some of the recent studies dealing with non-Q-AMI[4-7,9-11] hint that these non-Q-AMI patients are more likely to have jeopardized myocardium and that this jeopardized myocardium is responsible for the increased early and late reinfarction and late sudden cardiac death. Although a definitive answer is lacking, aspirin and dipyridamole[8] and diltiazem[17] may be effective in reducing reinfarction, if not mortality, in non-Q-AMI patients.

In the analysis of CAST mortality data, Echt et al[16] point out that while mortality is higher in the flecainide/encainide group, the secondary end points of nonfatal reinfarction and unstable angina are higher in the placebo group. These observations suggest that these agents exert a deleterious effect on ischemic myocardium. Then, if ischemic events are more likely to occur in non-Q-AMI, the mortality would be expected to increase. Our data suggest that in non-Q-AMI patients, interaction with encainide/flecainide resulted in an increased death rate which could have spuriously reduced the apparent reinfarction rate. Thus, we believe our results also suggest that nonfatal myocardial infarction should not be used by itself as a study end point — as recently recommended by Fleiss et al.[18]

Whereas our study appears to be the first to show that in humans interaction of encainide/flecainide with non-Q-AMI led to a greatly increased risk of cardiac death, potentially lethal proarrhythmia effects from encainide/flecainide during early postmyocardial infarction have been demonstrated in animals.[19,20] For instance, O-demethyl encainide, a potent metabolite of encainide, caused not only a concentration-dependent decrease in ventricular fibrillation threshold but also an inability to defibrillate ventricular fibrillation in dogs with a myocardial infarction of about 2 days old.[20] Similarly, flecainide in the presence of myocardial ischemia occurring 4 to 7 days after anterior myocardial infarction in dogs frequently caused ventricular fibrillation and sudden death.[19]

Study limitations: There are a few shortcomings in our study. Prior myocardial infarction was observed in about one-third of our patients. This may be a part of the reason why, in contrast to the recent data from the Multicenter Diltiazem Post-Infarction Group,[21] in the placebo group of our study non-Q-AMI patients had a much lower death and cardiac arrest rate than Q-AMI patients. A relatively infrequent rate of events precluded further analyses limited only to those having no prior myocardial infarction.

Problems associated with the post hoc subgroup analyses are well recognized.[22] Our data originated from such analyses including "multiple looks," which might have given rise to spurious findings resulting from random variation. Our results therefore must be interpreted with caution and need to be confirmed by future clinical trials. However, we believe that our findings are consistent with the previous clinical and animal experimental results: Non-Q-AMI patients tend to have a higher reinfarction rate after hospital discharge than Q-AMI patients[2,4-11]; some of the animal studies[19,20] suggested that both encainide and flecainide precipitated potentially lethal ventricular arrhythmias in the presence of ischemic myocardium.

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Comparative Quantitative Angiographic Analysis of Directional Coronary Atherectomy and Balloon Coronary Angioplasty

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An attempt to assess the "utility" of directional atherectomy was made using a new quantitative angiographic index. This index can be subdivided into an initial gain component and a restenosis component. The initial gain index is the ratio between the gain in diameter during intervention and the theoretically achievable gain (i.e., reference diameter). The restenosis index is the ratio between the decrease at follow-up and the initial gain during the procedure. The net result at long-term follow-up is characterized by the utility index, which is the ratio between the final gain in diameter at follow-up and what theoretically could have been achieved. For this purpose, 30 coronary artery lesions were selected from a consecutive series of successfully dilated primary angioplasty lesions and were matched with the initial 30 successfully treated primary atherectomy lesions. Matching by location of stenosis and reference diameter resulted in 2 comparable groups with identical preprocedural stenosis characteristics. Atherectomy resulted in an increase in minimal luminal diameter 2 times larger than angioplasty (1.53 vs 0.77 mm; p <0.0001). However, at follow-up there was a significant decrease in minimal luminal diameter and a significant increase in percent diameter stenosis in the groups with atherectomy and angioplasty (1.69 ± 0.58 vs 1.57 ± 0.58 mm, p = not significant [NS], and 37 ± 18 vs 47 ± 18%, p = NS respectively). The decrease in minimal luminal gain was more pronounced in the group with atherectomy than in that with angioplasty (0.92 ± 0.69 vs 0.35 ± 0.51 mm; p = 0.0005). Consequently, directional atherectomy resulted in a significantly higher initial gain ratio than did balloon angioplasty (0.84 vs 0.41, p <0.00001). At follow-up, restenosis and utility ratios were comparable in both groups (0.56 vs 0.62, p = NS, and 0.29 vs 0.23, p = NS, respectively). In matched groups, directional atherectomy is a very effective device with a substantially better initial result than that with balloon angioplasty. However, it appears to be a potent stimulator of the restenosis process, because at follow-up this initial favorable result is lost, and the minimal luminal diameter is comparable to that after balloon angioplasty. Thus, the final utility of directional coronary atherectomy is not significantly different from that of conventional balloon angioplasty.

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Restenosis after conventional balloon angioplasty remains the major limitation of this procedure.[1–5] Despite extensive efforts to elucidate this phenomenon, our knowledge remains incomplete. In recent years studies have suggested that intimal hyperplasia is the major mechanism responsible for restenosis[6–9] and that lesion characteristics and regional flow dynamics influence this proliferative process.[10] Because improved operator experience and angioplasty techniques have not caused a reduction in restenosis rates, interventional cardiologists have designed new devices aimed at debulking instead of dilating atherosclerotic plaque. Directional atherectomy is a new technique with the potential advantage of creating smooth luminal surface. However, early experience with atherectomy indicates that restenosis rates are comparable with those after conventional balloon angioplasty, although a randomized study has not been initiated.[11–13] Recently it has been demonstrated that the immediate results of atherectomy are superior to those achieved by balloon angioplasty[14]; whether this initial advantage can be maintained during follow-up and may ultimately result in a reduction of the restenosis rate needs to be

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assessed. Therefore, the present study was performed to determine whether this initial favorable result obtained with atherectomy affects the incidence of restenosis.

METHODS

Patient group: From September 1989 through January 1991, 66 patients underwent 74 atherectomy procedures. For the purpose of this study, the initial 30 consecutive patients (23 men and 7 women, mean age ± standard deviation 60.2 ± 10.1) who underwent an angiographically successful procedure (postprocedural diameter stenosis <50%, with tissue retrieval) of a primary lesion in a native coronary artery were selected. At the time of atherectomy, 16 patients were in New York Heart Association functional class IV, 7 in III and 7 in II. Coronary angiography showed 1-vessel disease in 25 patients, 2-vessel disease in 4 and 3-vessel disease in 1. The site of obstruction was located in the left anterior descending coronary artery in 18 patients, the right coronary artery in 7 and the circumflex artery in 5.

Atherectomy procedure: After administration of local anesthesia, an 11Fr sheath was inserted in the femoral artery. All patients received 250 mg of acetylsalicylic acid and 10,000 U of heparin intravenously. Intracoronary injection of isosorbide dinitrate was performed to optimally vasodilate the vessel. After initial angiograms in multiple views were obtained, a special 11Fr guiding catheter was placed into the ostium of the coronary artery. Under fluoroscopy, the guidewire was advanced in the distal part of the artery. Then, the atherectomy device was directed over the guidewire and positioned across the stenosis. The support balloon was then inflated up to 0.5 atm, the cutter was retracted and balloon inflation pressure was increased to 2 to 3 atm. The driving motor was activated, and the rotating cutter was slowly advanced to cut and collect the protruding atherosclerotic lesion in the collecting chamber located at the tip of the catheter. After every pass, the balloon was deflated and either removed or repositioned. On average, 6.7 ± 2.9 passes in multiple directions were performed across a stenosis. Atherectomy was considered successful when the residual stenosis was <50% after tissue retrieval. After atherectomy, the arterial and venous sheaths were usually left in place for 6 hours. Patients were monitored for 24 hours, and electrocardiograms and cardiac enzyme levels were obtained twice daily. Nifedipine was administered every 2 hours for 24 hours after the procedure, and the patients were administered aspirin for 1 year.

Follow-up evaluation: After successful atherectomy or angioplasty (i.e., <50% postprocedural diameter stenosis on visual inspection), patients were examined at the outpatient clinic. The follow-up coronary angiogram was obtained within 2 weeks after an exercise test. Angiography was performed earlier if symptoms occurred within 6 months.

Quantitative coronary angiography: Quantitative analysis of the coronary segments was performed with the computer-based Coronary Angiography Analysis System (CAAS), previously described in detail.[4,5,15,16] In essence, boundaries of a selected coronary artery segment were detected automatically from optically magnified and video-digitized regions of interest (512 X 512 pixels) of a cineframe. The absolute diameter of the stenosis in millimeters was determined using the guiding catheter as a scaling device. Each individual catheter was measured with a micrometer and used as a scaling device. Correction for pincushion distortion was performed. The computer-estimation of the original dimension of the artery at the site of the obstruction was used to define the interpolated reference diameter. The percentage diameter and area stenosis, as well as the cross-sectional area (mm^2), were then calculated.

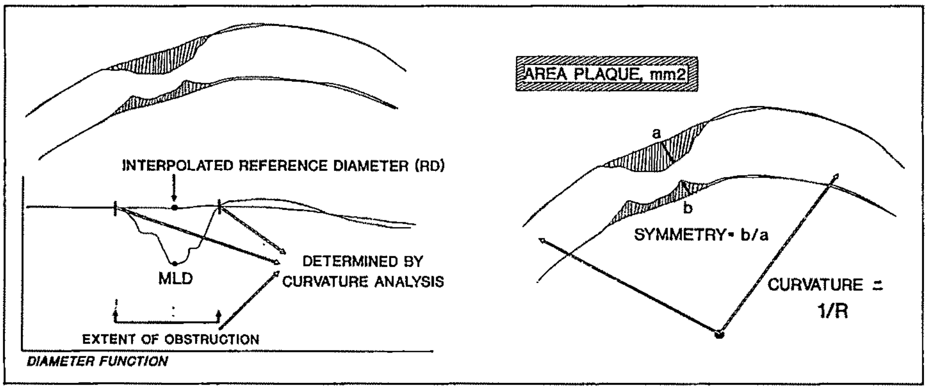

FIGURE 1. Graphic illustration of stenosis parameters obtained by quantitative coronary analysis. *Left,* y axis represents reference diameter, and vessel length is represented along x axis. Reference diameter and lesion length are determined by diameter at bounderies of lesion that are defined by curvature analysis. *Right,* curvature analysis is described. Curvature is defined by rate of change of angle through which tangent of curve turns, and which for a circle is equal to reciprocal of radius (R). MLD = minimal luminal diameter.

The length of the lesion (mm) was determined from the diameter function on the basis of curvature analysis (Figure 1). Symmetry was defined as the coefficient of the left-hand distance between the reconstructed interpolated reference diameter and actual vessel contours, and the right-hand distance between the reconstructed and actual contours at the site of the obstruction. Symmetry index ranged from 0 (totally eccentric stenosis) to 1 (symmetric). The degree of coronary bend was assessed by the curvature value at the obstruction site. This parameter was computed as the average value of all individual curvature values along the centerline of the coronary segment, with curvature defined as the first derivative of the tangent as it moves along the centerline, which for a circle is equal to the reciprocal of the radius. The area between the actual and reconstructed contours at the obstruction site was defined as the area plaque (expressed in mm^2). To standardize the method of analysis of the interventional and follow-up angiograms, the following measures were taken[16]: First, the x-ray system was exactly positioned, as was noted at the time of the intervention. Second, all study frames to be analyzed were selected at end-diastole to minimize foreshortening. Third, the investigator-determined beginning and end point of a segment of a major coronary artery were identified according to the definitions of the American Heart Association.[17] Finally, Polaroid photographs were taken of the video image with the detected contours superimposed to ensure that the analysis was performed on the same coronary segments in consecutive angiograms. Patients with balloon angioplasty were enrolled in ongoing restenosis trials, and therefore, according to the protocol, systematically received intracoronary nitroglycerin before and after angioplasty, and during follow-up catheterization, whereas patients with atherectomy were less frequently administered intracoronary nitroglycerin at recatheterization.

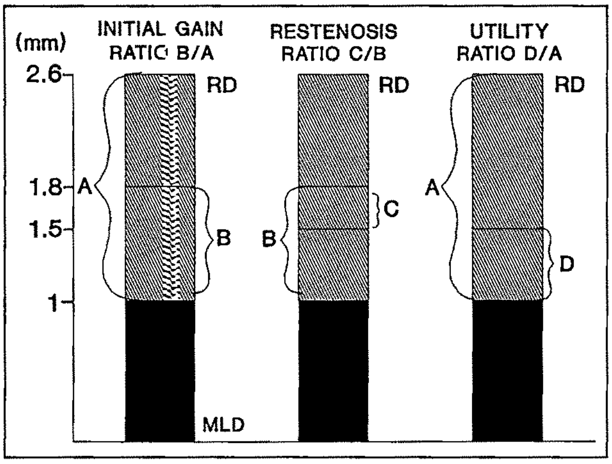

FIGURE 2. Graphic illustration of principle of initial gain, restenosis and utility indexes. Initial gain index is represented by the ratio B/A, restenosis index by C/B, and utility index by D/A. A = maximal achievable increase in minimal luminal diameter (MLD); B = gain in MLD during procedure; C = reduction during follow-up; D = long-term result; RD = reference diameter.

Restenosis: Two different criteria were used to define the restenosis rate. We have found a change in minimal lumen diameter ≥0.72 mm to be a reliable indicator of angiographic progression of vessel narrowing.[4,15,16] This value takes into account the limitations of coronary angiographic measurements and represents the long-term variability for repeat measurements of a coronary stenosis using CAAS. The second criterion for restenosis chosen was an increase in the diameter stenosis from <50% after intervention to ≥50% at follow-up. This criterion was selected because clinical practice continues to assess lesion severity by percent stenosis.

Assessment of initial gain, restenosis and utility ratio: To compare the relative efficacy of various interventional techniques, it is critical to relate the procedural outcome and changes during follow-up to the maximal achievable result. Therefore we propose the use of the aforementioned ratios in the evaluation of intracoronary interventions. Briefly, quantitative angiographic changes after intracoronary intervention may be divided in 3 stages (Figure 2). The first or "operational stage," is characterized by the interaction of the operational device with the lesion. In becoming operational, the diameter of the device may expand (directional atherectomy, balloon, stent) or maintain its original dimensions (laser, transluminal extraction catheter, rotational ablation). During this stage, the maximal effect of the device is achieved and determines to what extent the minimal luminal diameter may be increased. The initial gain index represents the ratio between the achieved luminal and maximal achievable luminal improvements (reference diameter minus minimal lumen diameter (MLD) before intervention), and is described by the following equation: initial gain index: change in MLD at intervention/reference diameter − MLD before intervention. The initial gain index ranges from 0 (no effect) to 1 (no residual stenosis). The second stage or "restenosis stage" begins during follow-up when biological processes determine the extent of intimal hyperplasia ultimately leading to a loss of luminal gain.

The restenosis index represents the ratio of decrease in luminal diameter improvement during follow-up and the achieved changes induced by intracoronary intervention, and is described by the following equation: restenosis index: MLD after intervention − MLD follow-up/change in MLD at intervention. The restenosis index ranges from 0 (initial benefit intact) to 1 (initial benefit completely lost).

The utility index represents the ratio of the net gain in lumen improvement at follow-up and the maximal achievable luminal improvement, and is described by the following equation: utility index: change in MLD at intervention – change in MLD at follow-up/reference diameter – MLD before intervention. The utility index ranges from 0 (no utility) to 1 (perfect result).

Matching process: The coronary artery tree was subdivided in 15 segments according to American Heart Association guidelines,[18] and the lesions were individually matched according to stenosis location and reference diameter. The principles of matching are threefold: the angiographic dimensions of matched lesions are assumed to be "identical," the observed difference between the 2 "identical" lesions must be within the range of CAAS reproducibility of 0.1 mm (1 standard deviation),[5] and finally, the reference diameters of the matched vessels are selected within a range of ± 0.3 mm (3 standard deviations; 99% confidence limits). To assess the immediate result of atherectomy and balloon angioplasty, 30 coronary artery lesions were selected by an independent technician (EMvS) from a consecutive series of successfully dilated balloon angioplasty lesions while complying with the selection criteria of matching. At the time of selection, the investigators were unaware of the 6-month angiographic outcome of these lesions. Matching was considered adequate if the mean difference of the reference diameter between the groups equaled 0 with standard deviation <0.3 mm.[19] Currently, the Thoraxcenter angiographic database contains quantitatively assessed stenosis data for 2,300 patients treated with either angioplasty (n = 1847), intracoronary stenting (n = 406), or directional or rotational atherectomy (n = 120).

Statistical analysis: All values are expressed as mean ± 1 standard deviation. Comparisons of the severity of minimal luminal diameter, area plaque, diameter stenosis, curvature value symmetry index and length between the groups were performed using analysis of variance and the unpaired Student's *t* test. Differences were considered statistically significant at $p < 0.05$.

TABLE I Matched Preprocedural Stenosis Characteristics of 30 Patients with Successful Coronary Atherectomy Compared with Successful Balloon Angioplasty

	Before Atherectomy	Before Angioplasty
Reference diameter (mm)	3.03 ± 0.57	3.07 ± 0.55
Minimal luminal diameter (mm)	1.08 ± 0.37	1.15 ± 0.36
Diameter stenosis (%)	64 ± 10	63 ± 8
Area plaque (mm^2)	9.5 ± 6.4	8.4 ± 3.6
Curvature value	15.9 ± 7.0	22.2 ± 13.1*
Symmetry index	0.6 ± 0.2	0.5 ± 0.3
Length	6.8 ± 2.7	6.5 ± 2.6

*p <0.02.

TABLE II Quantitative Comparison of the Immediate and Long-Term Results of Atherectomy and Balloon Angioplasty (n = 30)

	Atherectomy	Angioplasty	Unpaired *t* Test
Reference diameter (mm)			
Pre	3.03 ± 0.57	3.07 ± 0.55	NS
Post	3.24 ± 0.32	3.09 ± 0.56	NS
Follow-up	2.81 ± 0.57	3.04 ± 0.65	NS
Minimal luminal diameter (mm)			
Pre	1.08 ± 0.37	1.15 ± 0.36	NS
Post	2.61 ± 0.33	1.92 ± 0.31	0.0000
Follow-up	1.69 ± 0.58	1.57 ± 0.58	NS
Difference in minimal luminal diameter (mm)			
Post to pre	1.53 ± 0.47	0.77 ± 0.30	0.0000
Post to follow-up	0.92 ± 0.69	0.35 ± 0.51	0.0005
Diameter stenosis (%)			
Pre	64 ± 10	63 ± 8	NS
Post	19 ± 9	37 ± 10	0.0000
Follow-up	37 ± 18	47 ± 18	0.04
Difference in diameter stenosis (%)			
Pre–post	45 ± 12	26 ± 12	0.0000
Follow-up–post	18 ± 17	10 ± 17	NS

NS = not significant; Post = after intervention; Pre = before intervention.

RESULTS

Preprocedural stenosis characteristics of the matched patients are listed in Table I. Matching for stenosis location and reference diameter resulted in groups of patient with comparable severity of lesions. Matching was considered adequate because the reference diameter was equal in both groups (3.03 ± 0.57 vs 3.07 ± 0.55 mm; p = not significant), whereas the mean difference for this parameter between the groups was 0.0 mm (standard deviation 0.2 mm). Preprocedural minimal luminal diameter in the groups with atherectomy and angioplasty were 1.08 ± 0.37 and 1.15 ± 0.36 mm, respectively. The other stenosis parameters (diameter stenosis, area plaque, symmetry index and length) did not differ significantly, with the sole exception of curvature value, which was lower in the group with atherectomy than in that with angioplasty (15.9 ± 7.0 vs 22.2 ± 13.1; $p < 0.02$).

The immediate efficacy of atherectomy and angioplasty as assessed by quantitative angiography is shown in Table II and Figure 3. As expected, both atherectomy and balloon angioplasty significantly improved minimal luminal diameter (1.08 ± 0.37 to 2.61 ± 0.33 mm [$p < 0.0001$], and 1.15 ± 0.36 to 1.92 ± 0.31 mm [$p < 0.001$], respectively), but the increase in minimal luminal diameter was superior in the group with atherectomy than in that with angioplasty (1.53 vs 0.77 mm; $p < 0.0001$). Accordingly, the initial gain ratio of atherectomy was also superior when compared with that of angioplasty (0.84 ± 0.36 vs 0.41 ± 0.18; $p < 0.00001$). Thus, percent diameter stenosis was reduced from 64 ± 10 to 19 ± 9% ($p < 0.0001$) in the group with atherec-

TABLE III Quantitative Assessment of Initial Gain, Restenosis and Utility Ratios After Atherectomy and Balloon Angioplasty ($n = 30$)

	Atherectomy	Angioplasty	Unpaired *t* Test
Initial gain ratio	0.84 ± 0.36	0.41 ± 0.18	0.0000
Restenosis ratio	0.56 ± 0.55	0.62 ± 1.10	NS
Utility ratio	0.29 ± 0.33	0.23 ± 0.28	NS

NS = not significant.

tomy, and from 63 ± 8 to 37 ± 10% ($p < 0.001$) in the that with angioplasty.

At follow-up, all patients with atherectomy and angioplasty included in this study underwent 6-month control catheterization. Angiographic follow-up in the groups with atherectomy and angioplasty were 95 and 92%, respectively. Angiographic analysis at follow-up (Table II and Figure 4) showed a decrease in minimal luminal diameter in both groups (2.61 ± 0.33 to 1.69 ± 0.58 mm with atherectomy, 1.92 ± 0.31 to 1.57 ± 0.58 mm with angioplasty). Thus, the loss in minimal luminal diameter was more pronounced in the group with atherectomy than in that with angioplasty (0.92 ± 0.69 vs 0.35 ± 0.51 mm; $p < 0.0005$). Accordingly, percent diameter stenosis increased from 19 ± 9 to 37 ± 18% in the group with atherectomy, and from 37 ± 10 to 47 ± 18% in that with angioplasty. The concomitant restenosis and utility ratios are listed in Table III. Percent restenosis (detectable hyperplasia by quantitative coronary analysis) according to the 0.72 mm decrease in minimal luminal diameter (2 times the standard deviation of the long-term variability of the mini-

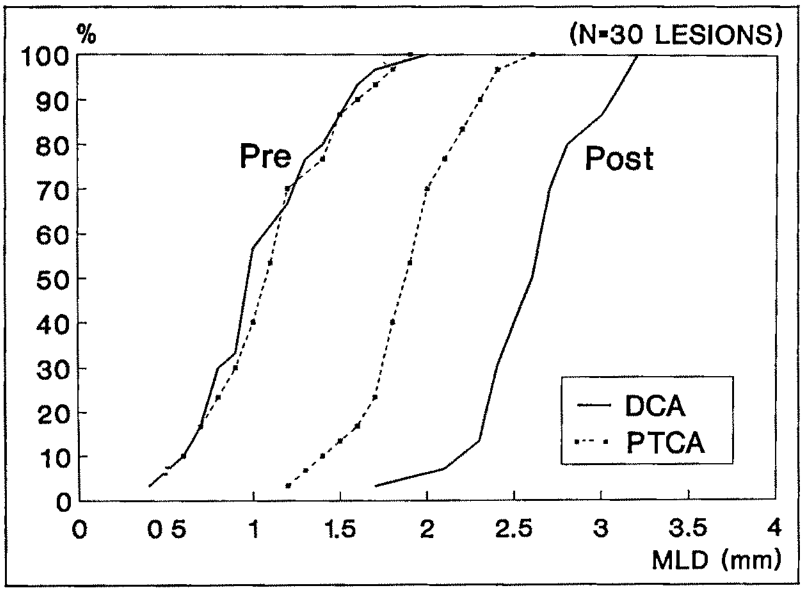

FIGURE 3. Cumulative frequency of immediate results of directional atherectomy (DCA) and balloon angioplasty (PTCA) in 30 matched lesions. Directional atherectomy resulted in an increase in minimal luminal diameter (MLD) from 1.08 to 2.61 mm, whereas angioplasty induced an increase from 1.15 to 1.92 mm. Post = after intervention; Pre = before intervention.

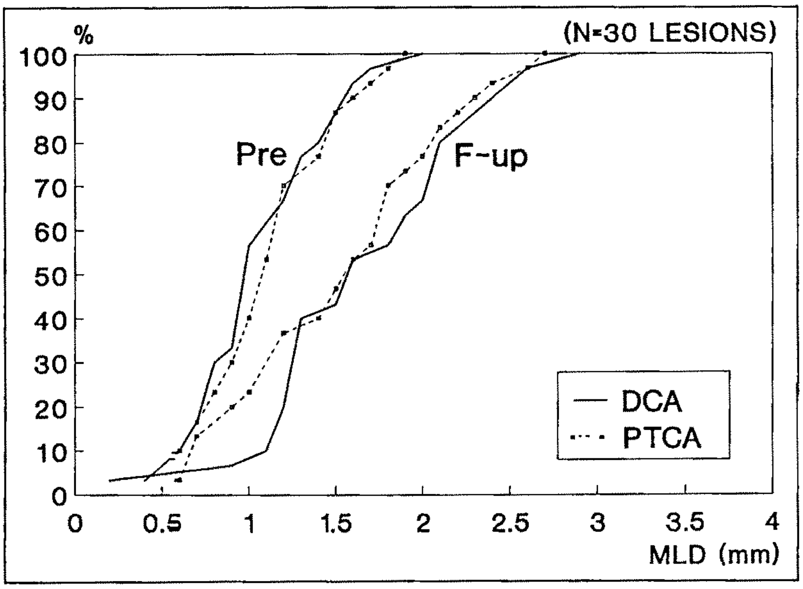

FIGURE 4. Cumulative frequency of long-term results of directional atherectomy and angioplasty in this matched population. At 6-month follow-up (F-up), initial favorable result of atherectomy is lost compared with that of balloon angioplasty. Other abbreviations as in Figure 3.

mal luminal diameter measurements using CAAS criterion) was 60% in the group with atherectomy versus 36% in that with angioplasty. When restenosis is defined by an increase in diameter stenosis ≥50% at follow-up, the restenosis percentages are 20 vs 16% (atherectomy vs angioplasty).

DISCUSSION

Coronary angioplasty is now an accepted form of treatment for patients with coronary artery disease. In the past, exponential growth in angioplasty has partly been the result of an increase patients returning with restenosis. Despite extensive efforts to improve catheter equipment we are still unable to effectively reduce the rate of restenosis. Because no fundamental design changes in balloon or balloon-derived catheter techniques are emerging, debulking techniques, such as directional atherectomy, have been introduced to improve the angioplastic process and to presumably reduce the rate of restenosis. The potential advantages of debulking atheromatous tissue over remodeling plaque with balloon angioplasty include: minimizing smooth muscle cell injury by wall stress; eliminating smooth muscle cells and thereby reducing their proliferative potential; improving regional blood flow and rheology by inducing fewer fissures or dissections; reducing radial stretch forces, as applied with a dilating balloon; and creating larger increases in minimal luminal diameter. Indeed, recent studies have reported a larger increment in luminal improvement after atherectomy than after conventional balloon angioplasty,[14] whereas other investigators observed a low incidence of postprocedural dissections.[11,12,14]

Study design: Whether atherectomy is superior to balloon angioplasty can only be assessed by a randomized study. This type of study would take several years, during which continuing refinements and improvements of catheter systems would take place, rendering the comparison unreliable and open to criticism. Therefore, we proposed a matching technique based on stenosis location and reference diameter to compare the results of various intracoronary interventional techniques. At present, this technique may be the best surrogate for a randomized trial when one tries to compare the short- and long-term results of atherectomy with those of conventional angioplasty. Using our matching program we selected comparable stenotic lesions with respect to baseline characteristics (minimal luminal diameter, diameter stenosis, length, area plaque and symmetry index) as assessed by quantitative angiography. This study group reflects the baseline stenosis characteristics in patients treated with atherectomy[20] or balloon angioplasty.[4,21]

Immediate results: This study confirms previous reports of improved luminal gain after atherectomy compared with that after conventional angioplasty.[14] Atherectomy resulted in a twofold increase in minimal luminal diameter (1.09 ± 0.37 to 2.61 ± 0.33 mm) compared with that with angioplasty (1.15 ± 0.36 to 1.92 ± 0.31 mm). Accordingly, percent diameter stenosis decreased more dramatically after atherectomy than after angioplasty. This improvement in luminal gain with atherectomy may be due to 3 mechanisms. First, introduction of the bulky device itself causes a lumen enlargement due to the "Dotter" effect. Second, the subsequent inflation of the support balloon may lead to further enlargement by stretching of the vessel wall. Finally, excision of the plaque determines the final result.

Restenosis: Recurrence of a stenosis after intracoronary intervention may be assessed by clinical symptoms, stress testing or coronary angiography. Because symptoms and functional achievement at exercise testing have low predictive values in regard to restenosis, diagnosis of restenosis should be based on reproducible quantitative angiographic measurements using a computer-assisted technique with either automated edge detection or videodensitometry. Furthermore, the definition of restenosis is a matter of ongoing debate. It has been shown by our investigative group,[4,22] as well as by others,[3] that the determination of the severity of stenosis using percent diameter stenosis does not reflect changes after angioplasty, because the adjacent part of the dilated vessel may also be involved in the restenosis process, or the reference diameter may be simultaneously reduced. Therefore, we selected minimal luminal diameter as a parameter for the morphologic changes after atherectomy or angioplasty. Minimal luminal diameter at follow-up was 1.69 mm for the group with atherectomy compared with 1.57 mm for that with balloon angioplasty ($p =$ not significant). These findings are similar to previously documented late follow-up studies of coronary balloon angioplasty (1.69 to 1.82 mm)[4] and stenting (1.68 mm).[23] Using the ≥50% diameter stenosis criterion, the rates of restenosis after atherectomy and angioplasty were 20 and 16%, respectively. Previous studies on restenosis after primary coronary atherectomy reported an incidence of restenosis of 20%[11,12] using the ≥50% criterion. Thus, during follow-up, the initial greater gain in luminal diameter after atherectomy compared with that after balloon angioplasty is totally lost. At follow-up, the reduction in minimal luminal diameter was 0.92 mm after atherectomy compared with 0.35 mm after angioplasty ($p = 0.0005$). Although minimal luminal diameter changed more dramatically in the group with atherectomy than in that with angioplasty, both had equal restenosis (0.56 vs 0.62; p = not significant) and utility (0.29 vs 0.23; p = not significant) ratios, indicating that the relative changes are equal for both interventional techniques.

Animal and atherectomy studies[11-13,20] have demonstrated that fibrointimal hyperplasia may develop in coronary arteries previously treated by balloon angioplasty or atherectomy. Pathologic findings have raised a theory that deeper vascular injury is associated with a greater intima proliferation. Injury beyond the subintimal level has been shown to be associated with more extensive intimal proliferation.[24] These data are supported by Webster et al[25] who found a greater smooth muscle proliferation after high-inflation pressure with the same balloon size when compared with that after low pressure. Furthermore, an initial follow-up study after atherectomy indicates that this process may be accelerated when deep vessel wall components such as media and adventitia are removed.[13] Additionally, atherectomy may lead to profound disrupture of the vessel wall architecture.[26] Finally, the introduction of the bulkier atherectomy device may potentially lead to a greater amount of vessel wall stretching compared with that with the smaller balloon catheter system. All these influences may account for the greater cellular proliferation of the lesion treated by atherectomy.

Study limitations: There are several limitations to this study. First, it is an uncontrolled, observational study limited to a subset of patients with successful coronary atherectomy or balloon angioplasty. This consecutive series of patients were studied by investigators unaware of the late angiographic results. Although matching for angiographic variables is a promising technique to assess the efficacy of intracoronary interventions, patient- and procedure-related variables are not included in the analysis. Second, lesion complexity was not incorporated in the analysis. This is usually defined qualitatively[27]; however, an objective and quantitative description of stenosis morphology has recently been introduced.[28] Further improvement in quantitative analysis may assess lesion morphology in a continuous scale fashion rather than assigning lesions to discrete categories. This type of analysis should be incorporated in future trials studying the efficacy of various interventional techniques. Third, this study is based on early experiences with atherectomy. Careful patient selection, future design changes and improved operator experience may further improve the immediate and long-term results. Thus, controlled clinical trials are needed in the future to determine the immediate angiographic results and long-term efficacy of these interventions, as well as the benefit, if any, to particular subgroups of patients. These studies should also address the presumed time frame for restenosis after any particular intervention.

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Clot-Selective Coronary Thrombolysis with Low-Dose Synergistic Combinations of Single-Chain Urokinase-Type Plasminogen Activator and Recombinant Tissue-Type Plasminogen Activator

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The effect of simultaneous infusions of low-dose recombinant tissue-type plasminogen activator (t-PA) and single-chain urokinase-type plasminogen activator (scu-PA, pro-urokinase) on coronary arterial thrombolysis was investigated in 23 patients treated within 6 hours (mean 2.6 ± 1.1, range 1.2 to 5.9) of symptoms of an acute myocardial infarction. Infarct artery patency at 90 minutes was achieved in 16 (70%, 95% confidence limits of 0.47 to 0.87) of 23 patients after a 1-hour intravenous infusion of 20 and 16.3 mg of t-PA and scu-PA, respectively. At 90 minutes, the fibrinogen concentration decreased from 369 ± 207 to 316 ± 192 mg/dl (p = not significant), while plasminogen decreased to 69 ± 24% (p = 0.001) and α-2-antiplasmin to 77 ± 24% (p = 0.001) of pretreatment values. Although no bleeding requiring termination of drug infusion or transfusion occurred, 1 patient with cerebrovascular amyloidosis had a fatal intracerebral hemorrhage. These findings suggest that combination therapy may allow substantial reductions in total thrombolytic doses while still achieving effective fibrin-specific coronary thrombolysis.

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Numerous clinical trials using both fibrin-selective or nonselective thrombolytic agents have demonstrated significant reductions in morbidity and mortality after acute Q-wave myocardial infarction.[1] Infarct artery patency rates at 90 minutes between 50 and 91% have been achieved with varying degrees of reduction in circulating fibrinogen and activation of the systemic thrombolytic system.[2]

Attempts to improve the overall recanalization rate, prevent early coronary reocclusion, and minimize perturbations in the systemic clotting system stimulate the ongoing quest for alternative treatment regimens. Recent studies have shown that the mechanism of action of the endogenous plasminogen activators, tissue-type plasminogen activator (t-PA) and single-chain urokinase-type plasminogen activator (scu-PA, pro-urokinase), are quite distinct[3] and that these mechanisms may act complementarily to produce synergistic lytic effects: t-PA binds to fibrin, undergoes a conformational change, and as a result manifests greater (more than 300-fold) catalytic efficiency as a plasminogen activator.[4,5] Scu-PA is more catalytically active against glu-plasminogen bound to fibrin than in solution.[3] In vivo synergism for thrombolysis has been demonstrated in both rabbit and dog models of intravascular thrombosis.[6–8] However, only limited information is available about the consequences of simultaneous infusions of both agents in patients with acute myocardial infarction. If such synergism occurred in patients, it might allow a significant reduction in the total dose of either agent needed for thrombolysis, thus lowering costs and potentially reducing the risks of bleeding. In this report, we describe the clinical results obtained after the coadministration of low-dose t-PA and scu-PA to 23 patients with acute myocardial infarction.

METHODS

This study was conducted by investigators from the following institutions: Brigham and Women's Hospital and Beth Israel Hospital, Boston, Massachusetts; The

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Johns Hopkins Hospital and St. Agnes Hospital, Baltimore, Maryland; Methodist Hospital, Indianapolis, Indiana; St. Elizabeth's Hospital, Boston, Massachusetts; Tufts-New England Medical Center, Boston, Massachusetts; and The University of Michigan Medical Center and St. Joseph's Hospital, Ann Arbor, Michigan.

Inclusion criteria: Patients aged 18 to 76 years with suspected acute myocardial infarction, characterized by chest pain lasting for $\geq$30 minutes, were screened for entry. The inclusion criteria included ST-segment elevation of 0.1 mV in at least 2 contiguous precordial leads or 2 limb leads and an interval $\leq$6 hours between the onset of symptoms and the start of the administration of the thrombolytic agent. The currently accepted contraindications for thrombolytic therapy were used as exclusion criteria.[9] In addition, patients with cardiogenic shock, percutaneous transluminal coronary angioplasty within 6 months, prior coronary artery bypass grafting, or any documented systolic pressure >180 mm Hg or diastolic pressure >110 mm Hg were excluded. The protocol was approved by each hospital's institutional review board, and all patients provided written informed consent before entry into the study.

Materials: Scu-PA (batch numbers V76/1 and V76/2) was supplied by Sandoz Research Institute, Hanover, New Jersey, in vials containing 500,000 IU of scu-PA in lyophilized form. The biologic origin of the scu-PA used was the human kidney cell line TCL-598 with a specific activity of 181,000 IU/mg. t-PA was obtained from Genentech, South San Francisco, California, as alteplase.

Study design: The study was designed as an open-label prospective trial. Upon enrollment, 2 peripheral intravenous access routes were established and patients immediately received a 5,000 IU heparin bolus. Thrombolysis was initiated with 20% of the customary recommended dose (20 mg) of t-PA administered intravenously as a 10 mg bolus followed by a 10 mg infusion over 60 minutes. Immediately after commencing the t-PA infusion, a 724,000 IU (4 mg) intravenous bolus of scu-PA followed by a 60-minute infusion of 2,226,000 IU (12.3 mg) were administered through a separate intravenous line. This represents approximately 20 to 25% of currently reported doses of scu-PA when used as monotherapy.[10] Heparin was begun at 1,000 IU/hour after completion of the t-PA/scu-PA infusions. The heparin dose was subsequently adjusted to maintain the partial thromboplastin time at 1.5 to 2 times control and continued for a minimum of 18 hours. Aspirin, 80 mg/day, was initiated on the day after thrombolytic therapy and continued until the heparin infusion ended at which time the dose was increased to 325 mg/day. All other medications, including antiischemic and antiarrhythmic agents, diuretics, analgesics and sympathomimetics, were administered as required. Blood samples for coagulation variables and routine chemistry and hematologic studies were obtained before and at 60, 90 and 240 minutes after initiation of thrombolytic therapy.

Coronary angiography using the Judkins technique was performed within 90 minutes in all patients. The initial infarct artery injection was assessed in the Coronary Angiography Core Laboratory according to the Thrombolysis in Myocardial Infarction Trial (TIMI)[9]: grade 0 no perfusion detected, grade 1 penetration of contrast without perfusion, grade 2 partial perfusion, and grade 3 complete perfusion. Patients graded 2 or 3 at 90 minutes after initiation of t-PA/scu-PA infusions were classified as responders, whereas those graded 0 or 1 were classified as nonresponders. Presumptive identification of the infarct-related artery was based on visualizing residual intracoronary thrombus or stenosis in the vessel supplying myocardium considered to be ischemic because of associated wall motion abnormalities on ventriculography or ST-segment elevation on the electrocardiogram.

Hematologic studies: Fibrinogen was measured by the sodium sulfite precipitation method.[11] Blood samples were collected in 13 mM trisodium citrate and 500 KIU/ml aprotinin (to prevent in vitro fibrinogenolysis), after which they were immediately cooled to 4°C. The samples were centrifuged at 800 g for 15 minutes to isolate plasma, which was then stored at −20°C for up to 6 weeks. Plasminogen and α-2-antiplasmin were measured using the chromogenic peptide substrate H-D-valyl-L-leucyl-L-lysyl-p-nitroanilide (S-2251) in plasma to which no aprotinin was added.[12] The fibrin(ogen) degradation products were measured according to the method of Mersky et al[13] in serum samples. Serial dilutions were performed on each serum sample until agglutination was no longer observed. Patient values are reported as the median of the range of the greatest dilution producing agglutination.[14]

Statistical methods: Values are expressed as means ± standard error of the mean in all cases. Mean values were compared using the student's *t* test, with $p \leq 0.05$ considered significant.

RESULTS

Twenty-three patients (13 men and 10 women) satisfied the eligibility criteria and were enrolled in the study. Mean age of the patients was 61 ± 10 years (range 33 to 75); average time from onset of chest pain to the administration of thrombolytic therapy was 2.6 ± 1.1 hours (range 1.2 to 5.8). All 23 patients had myocardial infarction as documented by elevated plasma levels of myocardial specific enzymes. The infarct-related artery was the left anterior descending coronary artery in 39% (9 of 23), right coronary artery in 52%

TABLE I Patient Characteristics

Age (year)	61 ± 10 (range, 33–75)
Men:women	13:10
Height (cm)	66 ± 4 (range, 56–73)
Weight (kg)	83.9 ± 22.3 (range, 51–157)
Time from symptom onset to thrombolytic treatment (hours)	2.5 ± 1.1 (range, 1.2–5.8)
Coronary artery occluded	
Left anterior descending	9/23 (39%)
Left circumflex	2/23 (9%)
Right	12/23 (52%)

TABLE II Effect of t-PA/scu-PA on Hematologic Parameters

Hematologic Parameter	Before Treatment	90 Minutes After Treatment
Fibrinogen (mg/dl)	369 ± 207	316 ± 192
Fibrin(ogen) degradation products (μg/ml)	1.4 ± 3.3	28.5 ± 42.9*
Plasminogen (% initial value)	100	69 ± 24*
Alpha-2-antiplasmin (% initial value)	100	77 ± 24*

*$p \leq 0.001$ compared with pretreatment value.
scu-PA = single-chain urokinase-type plasminogen activator; t-PA = tissue-type plasminogen activator.

(12 of 23) and the left circumflex coronary artery in 9% (2 of 23). Study population characteristics are described in Table I.

Infarct artery patency: A patent infarct vessel (TIMI grade 2 or 3) was present in 16 (70%) of 23 patients on the 90-minute angiogram. Two additional patients who were TIMI grade 0 or 1 at 90 minutes achieved TIMI grade 3 flow at 113 and 150 minutes. Thus the combination regimen of low-dose t-PA and scu-PA achieved successful infarct artery patency in 18 of 23 patients (78%).

In 10 patients, 60-minute angiograms were available. Two patients who were TIMI grade 2 at 60 minutes showed evidence of increasing intraluminal filling defects at 90 minutes associated with decreasing intracoronary flow to TIMI grade 0 and 1. Of the remaining 8 patients 7 had maintained infarct artery patency on both the 60- and 90-minute angiograms and 1 patient was unable to achieve patency on either angiogram.

After an additional 20 mg of intracoronary t-PA, coronary angioplasty was attempted without success in 2 patients with persistently occluded infarct vessels at 90 minutes. No patient required immediate coronary bypass surgery.

Hematologic studies: Hematologic parameters were measured before treatment with t-PA and scu-PA, and at 1, 1.5 and 4 hours after initiation of therapy. Adequate samples were available for measurement of these parameters in 17 of 23 patients. Peak effects of treatment were noted at 90 minutes, and were tending toward normal by 4 hours. Treatment had only a modest effect on plasma fibrinogen, producing a trend toward a decrease (15% reduction) that did not achieve statistical significance (Table II). Fibrinogen degradation products increased significantly at 90 minutes by $>$20-fold; plasminogen and α-2-antiplasmin both decreased significantly at 90 minutes by 31 and 23%, respectively.

Adverse reactions or bleeding complications: No bleeding episodes requiring termination of drug infusion or transfusion occurred. There were no specific reports of localized hematomas at either venipuncture or catheterization sites. Hemoglobin declined from 14.7 ± 0.1 g/dl before treatment to 12.2 ± 0.2 g/dl ($p \leq 0.001$) after cardiac catheterization.

The single hospital death related to thrombolytic drug infusion occurred in a 66-year-old man with an acute inferior Q-wave myocardial infarction. Six and one-half hours after initiation of drug infusion he became confused and subsequently unresponsive. Emergency-computed tomography of the brain confirmed an intraventricular and cerebral hemorrhage. Despite intensive supportive therapy, progressive hypotension ensued and he died 42 hours later. The patient had no clinical bleeding from other procedure sites including a radial artery puncture and femoral artery catheterization. He demonstrated no significant decline in fibrinogen or elevation in fibrin(ogen) degradation products, and his coagulation parameters remained well within clinically appropriate range with peak values (in seconds) of: protime 13.6, control 12.5; partial thromboplastin time 70.3, control $<$30; thrombin time 20, and control $<$25. Postmortem examination confirmed significant coronary and cerebral arteriosclerosis, patent coronary arteries and diffuse cerebral microvascular amyloidosis. Hemorrhagic foci were predominantly noted at sites of the cerebral amyloid angiopathy.

DISCUSSION

The last 10 years bear witness to a remarkable evolution in medical management strategies for treating acute myocardial infarctions. The observations of DeWood et al[15] that virtually all Q-wave myocardial infarctions are precipitated by occlusive coronary thrombosis have stimulated several now familiar clinical trials that have convincingly demonstrated significant reductions in mortality when patients receive early intravenous thrombolytic therapy. It is generally agreed that the predominant mechanism of action of these agents is rapid lysis of the obstructing intracoronary thrombus.[1]

Concerns regarding increased bleeding risks, limitations of invasive procedures performed soon after thrombolysis and high costs may inhibit the use of these drugs. Efforts to enhance efficacy and broaden applicability of thrombolytic therapy include using "front-loaded" t-PA dosing regimens, genetically engineered drug mutants that have prolonged half-lives or enhanced fibrin-specificity, various combinations of thrombolytic and antiplatelet agents or, more recently, thrombolytic and selective antithrombin agents.[16-18] This study demonstrates the feasibility of low-dose synergistic combinations of t-PA and scu-PA in achieving a satisfactory infarct-artery patency rate with only minimal effects on systemic clotting parameters.

The combination of scu-PA and t-PA has shown significant synergism in vitro as well as in both rabbit jugular vein and dog coronary artery thrombosis in vivo models.[3,6-8] The concentration range in which synergism is observed is 15 to 25% of the minimum thrombolytic dose of each drug used alone. Recently, Collen and Van de Werf[19] reported that combined infusions of t-PA and scu-PA at monotherapy doses of 10% produced rapid coronary clot lysis in 7 of 9 patients, although Tranchesi and colleagues[20] failed to demonstrate effective clot lysis at slightly larger doses. In a larger study, Bode et al[21] administered 12 mg of t-PA and 48 mg of scu-PA to 38 patients with acute myocardial infarction and demonstrated an 81% infarct artery patency rate at 90 minutes. No unusual adverse effects have been reported in combination trials of t-PA and scu-PA.

The patency rates of 70% at 90 minutes and 78% overall presented in this study compare favorably with the best results reported in the other thrombolytic combination trials with t-PA and streptokinase (75%), scu-PA and urokinase (65%) and t-PA and urokinase (73%).[22-24] Intravenous monotherapy regimens with t-PA, streptokinase, anisoylated plasminogen streptokinase activator complex or scu-PA generally are associated with patency rates of 60 to 75%. A perfusion rate approaching 90% was recently reported using a "front-loaded" regimen with the traditional 100 mg dose of t-PA.[16]

Early studies indicate that an initial lag phase precedes the lytic activity of scu-PA but not that of t-PA.[25] Pannell et al[3] and Gurewich[26] believe that scu-PA principally activates glu-plasminogen after it has undergone a specific conformational change induced by binding to C-terminal lysine residues in fibrin. These become available only after clot degradation has been initiated by plasmin elaborated from glu-plasminogen by the actions of clot bound t-PA. By contrast, t-PA preferentially activates plasminogen bound to intact fibrin, thereby initiating fibrin degradation and creating C-terminal lysines and also providing the plasmin required to activate scu-PA to urokinase on the fibrin surface. The 2 activators are therefore complementary in that they activate different fibrin-bound plasminogen. This complementary mechanism of action is believed to explain their synergy.

Minimal depression of fibrinogen levels were noted in this study, suggesting that the use of these agents in doses that alone have little efficacy can, in combination, achieve considerable infarct artery patency with preservation of relative fibrin selectivity. Larger trials will need to verify that this is not confounded by an increased reocclusion rate.

A low incidence of adverse reactions was found in these patients. Despite the performance of cardiac catheterization during or immediately after the drug infusion, there was no bleeding necessitating blood transfusion or termination of therapy. One patient had guaiac positive emesis. The single death directly related to drug therapy occurred in a patient with previously undiagnosed cerebral microvascular amyloidosis, a condition associated with an increased risk of spontaneous intracerebral hemorrhage. Although studies have failed to demonstrate a reduced incidence of bleeding with relatively fibrin-specific agents, this may in part be due to the loss of fibrin specificity at therapeutically effective doses. Larger trials are needed to determine if the smaller hemostatic perturbations associated with low-dose, combination therapy will translate into reduced bleeding or safer performance of urgent invasive or surgical procedures.

This pilot study suggests that a combination of one-fifth standard dose t-PA and scu-PA results in a near maximal rate of infarct artery patency with minimal associated perturbations in the hemostatic system. As in the other combination thrombolytic trials, the regimen reported here included concurrent full dose heparin, oral aspirin, and standard antiischemic medications including nitrates, calcium channel antagonists, and β blockers. Recent reports suggest the possible importance of concomitant intravenous heparin therapy to maintain infarct-artery patency in patients treated with t-PA, and for optimization of the effects of scu-PA when also used alone; our results must be considered with this in mind.[27-29]

The limited number of patients studied precludes drawing conclusions about the additional role of rescue percutaneous transluminal coronary angioplasty when combination thrombolytic regimens are unsuccessful. Two patients with persistent occlusion at 90 minutes underwent urgent percutaneous transluminal coronary angioplasty without success despite the additional use of intracoronary t-PA. Topol et al,[24] however, demonstrated improved patency and reduced mortality with rescue percutaneous transluminal coronary angioplasty in patients treated with combination t-PA and urokinase versus t-PA alone. Similarly, it is unclear if combination regimens will diminish the 15 to 20% early reocclusion rate demonstrated with single-agent therapy.[30] Interestingly, Grines reported a reocclusion rate of only 8% in patients treated with full-dose streptokinase and 50% t-PA.[22]

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APPENDIX

The Pro-Urokinase for Myocardial Infarction Study Group Study personnel: CLINICAL CENTERS: *Brigham & Women's Hospital and Beth Israel Hospital, Boston, Massachusetts:* James M. Kirshenbaum, MD, Principal Investigator, J. Anthony Ware, MD, Co-Investigator, Douglas E. Vaughan, MD, Co-Investigator, Donna Maciak, RN, Coordinator; *Methodist Hospital of Indiana:* Richard R. Schumacher, MD, Principal Investigator, Russell Valentine, MD, Co-Investigator, Richard Wenzler, MD, Co-Investigator, Sherry Kerner-Slemons, RN, BS, Coordinator; *The Johns Hopkin's Hospital and St. Agnes Hospital (Paul Dudley White Coronary Care System), Baltimore, Maryland:* John Flaherty, MD, Principal Investigator, Raymond D. Bahr, MD, Principal Investigator, Richard J. Bouchard, MD, Co-Investigator, Stephen J. Plantholt, MD, Co-Investigator, Anil Fatterpaker, MD, Co-Investigator, Eduardo Marban, MD, PhD., Co-Investigator, Frank C.P. Yin, MD, PhD., Co-Investigator, Susan N. Townsend, RN, BS, Coordinator; *Tufts New England Medi-*

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HEMATOLOGY CORE LABORATORY: *Brigham & Women's Hospital, Boston, Massachusetts:* Joseph Loscalzo, MD, PhD, Director, Dorinda George, AB, Senior Technician.

ANGIOGRAPHY CARE LABORATORY: *Brigham & Women's Hospital, Boston, Massachusetts:* James M. Kirshenbaum, MD, Director, Peter Ganz, MD, Co-Director.

Effectiveness of Double Bolus Alteplase in the Treatment of Acute Myocardial Infarction

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Fifty-nine consecutive patients presenting within 6 hours of the onset of symptoms of an acute myocardial infarction were treated with 150 mg of soluble aspirin orally, and either 70 or 100 mg of alteplase divided into 2 intravenous bolus injections separated by 30 minutes. Dosage regimens were either 20 followed by 50 mg (group A), 50 followed by 20 mg (group B), or 50 followed by 50 mg (group C). Coronary angiography 60 minutes after the first bolus showed infarct-related coronary artery patency (Thrombolysis in Myocardial Infarction score 2 or 3) in 13 of 16 (81%) patients in group A, 12 of 17 (71%) in group B, and 10 of 11 (91%) in group C (overall patency rate at 60 minutes: 35 of 44 [80%] patients; 95% confidence interval 68 to 91%). At 90 minutes, patency rates were 15 of 20 (75%) patients in both groups A and B, and 18 of 19 (95%) in group C (overall patency rate 48 of 59 [81%] patients; 95% confidence interval 72 to 91%). Residual thrombus was identified with the 90-minute angiogram in 7 patients in group A, 5 in group B, and 3 in group C. Although there was no statistically significant difference in patency between the 3 dosage regimens at either 60 or 90 minutes there was a trend toward increased patency and more complete thrombolysis at 90 minutes in group C. No episodes of bradyarrhythmia, hypotension or cerebrovascular bleeding were observed after double bolus therapy. There were 7 episodes (12%) of reocclusion, and 3 deaths (5%) within 1-month follow-up. Double bolus alteplase therapy is a convenient and highly effective method of promoting early coronary artery patency.

(Am J Cardiol 1991;68:1570–1574)

The efficacy of a 3-hour infusion of 100 mg of recombinant tissue-type plasminogen activator (rt-PA) in acute myocardial infarction is well-established. Using this regimen, infarct-related coronary artery patency (Thrombolysis in Myocardial Infarction [TIMI] score 2 or 3) is achieved in 71% of patients 90 minutes after beginning treatment.[1,2] When administered within 5 hours of the onset of symptoms of acute myocardial infarction, this regimen preserves left ventricular function, and reduces infarct size and mortality.[3] Recently, interest has been shown in front-loaded dosage regimens of alteplase (predominantly 1-chain rt-PA) with the aim of promoting early infarct-related coronary artery patency and improving myocardial salvage.[4] In this study we investigated the effect of administering a total dose of either 70 or 100 mg of alteplase divided into 2 bolus injections separated by 30 minutes.

METHODS

Sixty consecutive patients were admitted to the coronary care unit of the Regional Medical Cardiology Centre through the mobile coronary care unit, accident and emergency department, or cardiac ward between February and August 1990. Patients were enrolled in the study if they had chest pain of ≥30 minutes and ≤6 hours duration, were aged between 18 and 75 years, and had electrocardiographic changes consistent with acute myocardial infarction (ST-segment elevation ≥1 mm in 2 precordial or 2 inferior leads).

Patients were excluded if they had a history of bleeding diathesis, recent surgery or trauma, significant hypertension (>180 mm Hg systolic or >110 mm Hg diastolic pressure), any cerebrovascular event, diabetic retinopathy, active peptic ulceration or any condition precluding coronary angiography or thrombolytic therapy. Patients were also excluded if they were of child-bearing potential, taking warfarin, nonsteroidal antiinflammatory drugs or aspirin, had electrocardiographic or historical evidence of myocardial infarction in that territory, or had an electrocardiogram showing left bundle branch block.

The protocol was approved by the research ethical committee of the Faculty of Medicine of the Queen's University of Belfast. Informed consent was obtained

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from the patients or their relatives before administration of thrombolytic therapy.

Three dosage regimens were chosen to investigate the effect of a total dose of either 70 or 100 mg of alteplase (Boehringer Ingelheim Ltd.) and differentiate between the effects of an initial bolus of either 20 or 50 mg of alteplase (Figure 1).

All patients received intravenous diamorphine for pain relief and were monitored continuously. Two intravenous cannulas were inserted into opposite forearm veins for drug administration and blood sampling, respectively. Blood samples were obtained before administration of the first bolus, then 90 minutes later and then daily for 3 days. Five milliliters of whole blood were collected at baseline and daily thereafter for creatine kinase assay for 3 days, and plasma samples were collected at 0 and 90 minutes in citrated tubes for estimation of fibrin D-dimer levels using an enzyme-linked immunosorbent assay kit. After receiving a 150 mg tablet of soluble aspirin, patients were randomized to receive either 20 mg of alteplase as an intravenous bolus delivered over 3 to 5 minutes followed by a 50 mg bolus 30 minutes later (group A), 50 followed by 20 mg (group B), or 50 followed by 50 mg (group C) (Figure 1).

Randomization was achieved by allocating dosage in random sequence to numbered packs that were used consecutively.

The primary end point of this study was infarct-related coronary artery patency 90 minutes after the first bolus injection (angiogram 1). Secondary end points were patency at 60 minutes (angiogram 0) and at 19 to 48 hours (angiogram 2), and all clinical events occurring up to 1 month after treatment.

Coronary angiography was performed by the Judkin's technique, and patency was assessed according to TIMI score (0 or 1 = no reperfusion; 2 or 3 = patent artery).[2] In all cases, grading was performed on the first coronary injection. If the infarct-related artery was occluded at 60 minutes, no further injections were performed until 90 minutes. No heparin was administered until after the 90-minute angiogram. Five thousand units of heparin were then administered intravenously to patients with patent coronary arteries (TIMI score 2 or 3), followed by an intravenous infusion of heparin at 1000 U/hour. Patients who did not reperfuse at 90 minutes received a 30 mg intravenous infusion of alteplase over 90 minutes, followed by the intravenous heparin regimen (groups A and B only), or underwent mechanical probing of the obstruction, followed by heparin (group C). Thus, in no case did the total dose of alteplase exceed 100 mg.

Early reocclusion was assessed by coronary angiography 19 to 48 hours after the first bolus injection. Patient management after the 90-minute angiogram was selected by the initial investigator. Angiograms were subsequently reviewed and graded by 2 investigators who were unaware of the dose regimen given (GCP and CMW).

Reperfusion grades for the different dosage regimens were examined using the chi-square test for association. The conventional 5% level of statistical significance was adopted as standard.

RESULTS

Study patients: Sixty consecutive patients were treated. One hypoxic (arterial oxygen pressure 5 kPa), confused patient was excluded because her symptoms were subsequently found to be of 12 hours duration (this patient had a patent coronary artery 60 minutes after treatment). Thus, 59 patients (45 men and 14 women, mean age 59 years, range 29 to 75) were included in the analysis. Twenty-four patients had anterior and 35 had inferior infarctions by the electrocardiographic criteria previously defined. In 8 cases with clearly defined electrocardiographic changes of acute myocardial infarction, the peak serum level of creatine kinase did not increase to greater than twice the upper limit of normal for our laboratory (normal = 145 U/liter).

Median delay from onset of symptoms to first bolus injection was 130 minutes (range 55 to 355). Thirty-six patients received the first bolus outside the hospital from mobile coronary care unit staff (median delay from onset of symptoms to treatment 122 minutes, range 55 to 240). Twenty-one patients received the first bolus at the accident and emergency department, and 2 were treated in the cardiac ward. The demographic details of the study population are listed in Table I.

D-dimer assay: Mean (± standard deviation) baseline concentrations of fibrin d-dimer in the 3 groups

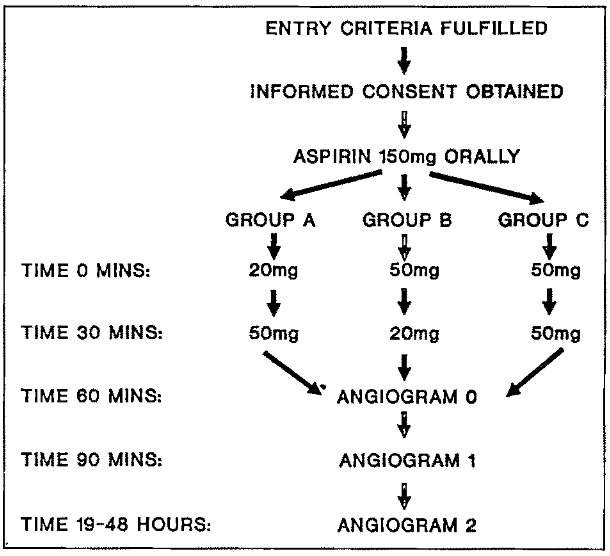

FIGURE 1. Double bolus alteplase study regimen.

TABLE I Demographic Details of the Study Group

	Group A	Group B	Group C
No. of pts.	20	20	19
Mean age (yr)	57	61	58
Sex (men)	15	16	14
Mean height (cm)	170	168	166
Mean weight (kg)	77	71	72
Mean initial heart rate (min^{-1})	77	75	72
Mean initial blood pressure (mm Hg)	125/75	123/77	120/69
Median delay onset of symptoms to first bolus (min)	135	122	130

were: group A, 101 ± 62 ng/ml; group B, 119 ± 53; and group C, 109 ± 68. These levels increased to 1,877 ± 1,082, 2,[illegible]0 ± 1,342 and 2,685 ± 1,410 ng/ml, respectively, at 90 minutes (p = not significant).

Angiographic data: Coronary angiography was performed in 44 patients at 60 minutes after the first bolus injection (angiogram 0). Coronary artery patency (TIMI score 2 or 3) was seen in 13 of 16 (81%) patients in group A, 12 of 17 (71%) in group B, and 10 of 11 (91%) in group C. Among patients with patent vessels (TIMI score 2 or 3) at 60 minutes, residual thrombus was seen in 5 cases in group A, 3 in group B, and 2 in group C (Figure 2). There was no statistically significant difference in patency rates between the 3 groups at 60 minutes (chi-square = 2.25, p >0.05). The overall patency rate was 35 out of 44 patients (80%, 95% CI = 68 to [illegible]%).

Fifty-nine patients were studied at 90 minutes (angiogram 1). Patency (TIMI 2 or 3) was observed in 15 out of 20 (75%) patients in both Group A and Group B. In Group C, 18 out of 19 (95%) had patent coronary arteries (Figure 2). There was no statistically significant difference in patency among the 3 groups (chi-square = 3.18, p >0.05). The overall patency rate was 48 of 59 patients (81%; 95% confidence interval 72 to 91%).

Fifty-six patients returned for angiography between 19 and 48 hours after the first bolus (angiogram 2, mean delay 33 hours) (Figure 2). Two patients were too ill for repeat catheterization, and 1 needed femoral arterial surgery for a sheath transection. Among patients with patent coronary arteries at 90 minutes there were no reocclusions at repeat angiography in group A (despite the presence of residual thrombus at 90 minutes in 7 patients), and only 1 reocclusion in group B (residual thrombus was observed in this patient). In group C there were 3 patients with reocclusion within the first 48 hours (none of whom had residual thrombus at 90 minutes).

Of the 10 patients in groups A and B needing additional alteplase at 90 minutes, coronary artery patency (TIMI score 2 or 3) was achieved in 7 cases (3 in group A, and 4 in group B). The 1 patient in group C who underwent mechanical probing had a patent artery (TIMI score 3) 24 hours after the procedure (Figure 2).

One patient in group A reoccluded on day 5, and 2 in group C reoccluded on days 6 and 14, respectively. Thus, the total number of reocclusions was 7 (12%).

Nineteen patients (32%) underwent elective percutaneous transluminal coronary angioplasty within 6 weeks of study entry (1 needed emergency coronary artery bypass grafting for an unsuccessful procedure). Elective angioplasty was performed for high-grade residual stenosis (>90%) of the infarct-related coronary artery in all cases; of these 19 patients, the severity of

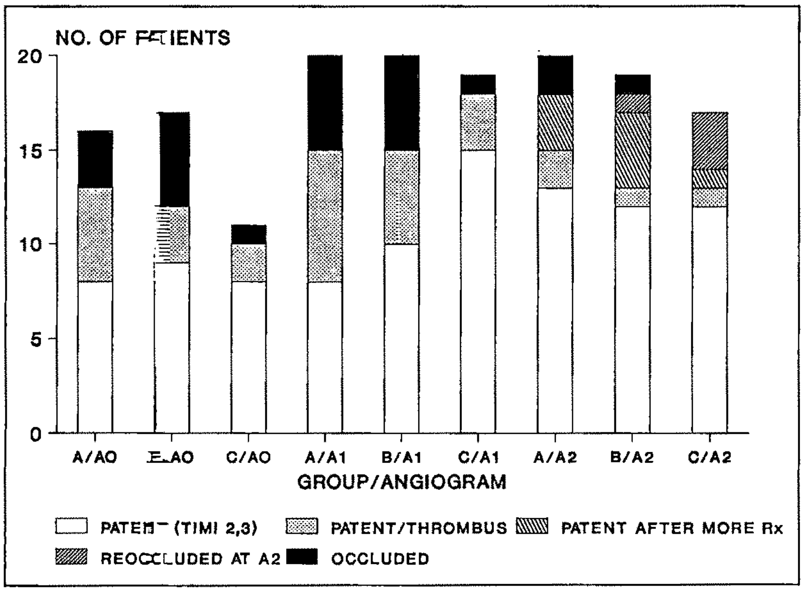

FIGURE 2. Outcome of infarct-related coronary artery at angiograms 0 to 2.
A = group A; A0 = angiogram at 60 minutes; A1 = angiogram at 90 minutes;
A2 = angiogram at 19 to 48 hours;
B = group B; C = group C.

the stenosis alone was the reason for the angioplasty in 11, there was continuing chest pain in 5, a strongly positive exercise stress test in 1, and coronary artery reocclusion had occurred in 2. Four patients (7%) have subsequently undergone elective coronary artery bypass grafting for severe 3-vessel disease and continuing symptoms (range 3 to 9 months).

Adverse events: In general, adverse events were minor (Table II). The most frequent bleeding complication was bruising at the arterial puncture site. One patient pulled his arterial sheath out and needed a transfusion of 1 unit of blood. In another case, a femoral sheath was transected by a Seldinger needle and embolized into the profunda femoris artery requiring operative removal and blood transfusion. Another patient with antithrombin III deficiency was found to have a hemoglobin level of 9 g/dl before treatment and was given 1 unit of blood after treatment.

One patient from each group developed gingival bleeding shortly after beginning thrombolytic therapy. In all 3 cases, this stopped spontaneously within 90 minutes. There was 1 episode each of hemoptysis and hematemesis. There were no cerebrovascular bleeding complications.

Arrhythmic events were infrequent. Three patients had episodes of ventricular fibrillation before bolus therapy. One patient needed direct current cardioversion for ventricular fibrillation after injection of radiographic contrast into the right coronary artery during the 60-minute angiogram. Another patient with intractable heart failure had ventricular fibrillation on day 15 before dying on day 16. Two patients needed intravenous antiarrhythmic therapy for sustained ventricular tachycardia within 8 hours of thrombolytic treatment.

In 7 patients, the initial rhythm was complete heart block (initial systolic blood pressure range 50 to 110 mm Hg). In all 7 patients, 1:1 atrioventricular conduction had returned by the 90-minute angiogram. None of these patients needed temporary pacing.

No patient developed bradycardia or hypotension (systolic blood pressure <80 mm Hg) after administration of either bolus of alteplase.

Three patients (5%) died. In addition to the patient who died from intractable heart failure, 1 died from a ventricular septal defect on day 2 before surgery could be instituted, and the third also developed a ventricular septal defect on day 2 and did not survive cardiopulmonary bypass after operative repair.

TABLE II Distribution of Adverse Events in the Study Group

	Group A	Group B	Group C
Femoral hematoma	3	6	5
Bleeding gums	1	1	1
Hematemesis	0	0	1
Hemoptysis	0	0	1
Sheath complication	0	0	2
Anemia	1	0	0
Ventricular tachycardia	0	1	1
Death	0	1	2

DISCUSSION

The rationale for bolus administration of rt-PA follows a report by Agnelli et al[5] in 1985 in which it was observed that despite its short plasma half-life rt-PA dissolves thrombus up to 4 hours after the end of an intravenous infusion. This finding was confirmed in patients with infarcts by Eisenberg et al.[6] Both studies attributed their findings to protection of rt-PA and plasmin from circulating plasma inhibitors by fibrin binding.

The first use of bolus rt-PA therapy in humans was reported by Khan et al.[7] A regimen of 4 bolus injections of 25 mg of duteplase administered at 20-minute intervals was compared with a 100 mg infusion. The acute recanalization rates (90-minute angiogram) were 79 and 58%, respectively, for bolus and infusion therapies (p = not significant). There was a trend toward earlier recanalization with bolus therapy (28 vs 39 minutes). In contrast to this multibolus technique, Verstraete et al[8] have investigated the efficacy of 1 large bolus injection of alteplase in patients with acute myocardial infarction and demonstrated 60-minute patency rates (TIMI score 2 or 3) ranging from 32 to 72% for doses of 50 to 70 mg. We adopted administration of a second intravenous bolus 30 minutes after the initial bolus (i.e., 7 plasma half-lives later), when plasma levels of alteplase should be <1% of peak levels.[9]

Our results show that high early patency rates (80% at 60 minutes) can be achieved by either 70 or 100 mg of double bolus alteplase. This result compares favorably with the 60-minute patency rates achieved by other thrombolytic agents and regimens (e.g., 48% for 1.5-megaunit infusion of streptokinase, 60% for 2-megaunit bolus of urokinase, and 74% for a 100 mg accelerated infusion of alteplase).[10-12] Although there was a trend in our study toward the 100 mg regimen at 60 minutes, no statistically significant difference in patency rates was demonstrated. Again, at 90 minutes there was no significant improvement in the high patency rates observed at 60 minutes (80 vs 81%) and no statistically significant difference between the 3 regimens was observed, although there was a trend toward group C. This suggests that the total dose of double bolus alteplase is the most important factor in determining patency at 90 minutes. Gemmill et al[13] obtained an 87% patency rate (TIMI score 2 or 3) at 90 minutes in 30 patients treated with 2 bolus injections of 35 mg of alteplase separated by 30 minutes. This result differs from our findings on total dose, but the numbers involved in both studies are small, and comparison should be made with caution. It is, however, apparent from both studies that early coronary patency can be achieved in a high percentage of patients by double bolus therapy.

Residual thrombus was observed in a patent vessel (TIMI score 2 or 3) at the 90-minute angiogram in 7 patients in group A, 5 in group B, and 3 in group C. This finding suggests that the rate of thrombolysis, as judged by patency and lack of residual thrombus, was greatest in group C, and least in group A. Support for this observation is found in the higher levels of fibrin d-dimer at 90 minutes in group B compared with that in group A (2,500 vs 1,877 ng/ml). Although not statistically significant, this result suggests more extensive lysis of cross-linked fibrin with the larger initial bolus.

There were 7 reocclusions (12%) during the course of this study. 5 occurred in group C. This is not unexpected in view of the high patency rate achieved in group C at 90 minutes (18 of 19 patients); 12 of 17 patients in this group were symptomatically free of reocclusion or reinfarction at 1-month follow-up. The rate of reinfarction with double bolus therapy was not greater than that associated with infusion therapy.[14] Heparin was not administered until after the 90-minute angiogram in this study, and earlier administration may have reduced thrombin formation and clot regeneration resulting in a lower reocclusion rate.[15] Delay in heparin administration did not lead to occlusion of the arterial sheath.

Bleeding complications observed were mostly minor and related to the arterial puncture site. Agnelli[16] suggested that rapid administration of rt-PA will cause less fibrinogenolysis and fewer bleeding complications than will infusion therapy owing to the rapid clearance of non–clot-bound rt-PA. No cerebrovascular bleeding occurred in the study population after the bolus administration of alteplase, nor did we observe significant bradycardia or hypotension. Interestingly, hemodynamic improvement occurred in all 7 patients with complete heart block. Early coronary reperfusion was associated with only 1 episode of ventricular fibrillation that may have been due to angiographic intervention alone.

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Relation of Technetium-99m Pyrophosphate Accumulation to Time Interval After Onset of Acute Myocardial Infarction as Assessed by a Tomographic Acquisition Technique

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Technetium-99m pyrophosphate (Tc-99m PYP) myocardial scintigraphy was performed in 110 clinically stable patients with acute or healed acute myocardial infarction (AMI). Tomography was performed 12 hours to 7 days (group A), 7 to 30 days (Group B), 1 to 6 months (Group C) and after >6 months (group D) after AMI. All 40 patients in group A, 9 of 31 in group B, 1 of 22 in group C, and no patient (0 of 17) in group D had a pathologic Tc-99m PYP tomogram. Relative Tc-99m PYP accumulation within the area of infarction was measured as infarct zone to blood pool ratio, which decreased significantly ($p < 0.001$) from group A (1.54 ± 0.39) to group B (0.89 ± 0.24), group C (0.8 ± 0.19) and group D (0.76 ± 0.13). These data were confirmed by sequential scintigraphy in 17 patients. It is concluded that a persisting Tc-99m PYP uptake is rarely found >1 month after AMI using tomographic imaging techniques in clinically stable patients with coronary artery disease. Positive results on Tc-99m PYP tomography are a reliable indicator of AMI. Thus, Tc-99m PYP tomography is not only a sensitive but also a specific imaging technique for AMI, which might be especially useful for diagnosis of reinfarction.

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Technetium-99m pyrophosphate (Tc-99m PYP) has been demonstrated to be a sensitive marker of acute myocardial infarction (AMI).[1–3] Tc-99m PYP scintigraphy, however, remaining persistently positive for at least up to 8 months, was reported to be frequently found with planar imaging technique.[4–6] The low specificity of the planar acquisition of Tc-99m PYP infarction scintigraphy, approximately 50 to 80%, reduces its value in the diagnosis of reinfarction.[5,7–9] Clinical studies have demonstrated tomographic acquisition to be superior to planar imaging in many respects.[10,11] However, whether persistent Tc-99m PYP accumulation after AMI is due to artifacts resulting from the planar acquisition technique or due to ongoing myocardial necrosis has not been solved. This study evaluates whether persistently positive Tc-99m PYP scintigrams may also occur in clinically stable patients using a tomographic imaging technique. A dual tracer myocardial scintigraphic imaging technique was used, combining Tc-99m PYP as a tracer for AMI and thallium (Tl)-201 as an anatomic marker for the myocardium.

METHODS

Myocardial scintigraphy was performed in 110 patients (mean age 54 ± 12 years, range 20 to 80) at various time points after AMI. Sequential myocardial scintigrams were recorded in a subset of 17 patients (Figure 1). Scintigraphy was performed in 40 patients 12 hours to 7 days after AMI (group A), in 31 patients after 7 to 30 days (group B), in 22 patients 1 to 6 months after infarction (group C), and in 17 patients after >6 months (group D). None of these patients had clinical evidence of subsequent AMI or persistent angina (symptoms, electrocardiography, creatine kinase).

The diagnosis of myocardial infarction was made when at least 2 of the following 3 criteria were fulfilled: (1) severe substernal chest pain unresponsive to nitrates during AMI, (2) elevation of total serum creatine kinase >70 U/liter with MB-isoenzyme fraction exceeding 7%, and (3) standard electrocardiographic criteria consistent with the diagnosis of AMI.[12]

Myocardial imaging: All patients were examined during a stable phase of their disease. Imaging was be-

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TABLE I Clinical Status and Scintigraphic Findings in the Four Groups Depending on the Time After Acute Myocardial Infarction

Group	No. of Pts.	Time After AMI	Anterior/ Inferior Infarction	Positive Studies	Uptake Ratio Tc-99m PYP*	Relative Size Tc-99m PYP* (segments)	Relative Size Tl-201 (segments)	Q/Non-Q-Wave Myocardial Infarction
A	40	3 ± 2 days	20/20	40	1.54 ± 0.39	2.73 ± 1.28	2.65 ± 1.55	33/7
B	31	17 ± 6 days	17/14	9	0.89 ± 0.24	0.90 ± 0.74	2.58 ± 1.11	25/6
C	22	3 ± 1 mos.	10/12	1	0.80 ± 0.19	0.84 ± 0.65	3.03 ± 1.72	21/1
D	17	3 ± 2 yrs.	10/7	0	0.76 ± 0.13	0.72 ± 0.50	2.51 ± 1.70	17/0

*Significant difference in group A compared with groups B, C and D ($p < 0.001$).
AMI = acute myocardial infarction; PYP = pyrophosphate; Tc = technetium; Tl = thallium.

gun 2.5 to 3 hours after intravenous injection of 90 MBq of Tl-201 and 200 to 370 MBq of Tc-99m PYP (Tecephos, Behringwerke Marburg). Scintigrams were recorded using a 38 cm large field-of-view camera (Dyna 4, Picker) with 2 impulse height analyzers. A commercial 7-pinhole collimator focused at 13.5 cm with 7 5.3 mm pinholes was fitted to the camera. Energy discrimination was provided by a 15% window centered on the 75 keV peak for Tl-201 and a 5% window centered on 140 keV for Tc-99m. This adjustment yields optimal results as shown in a previous study.[11] Seven-pinhole tomography was acquired as recently reported.[13]

Scatter corrections: The raw data were corrected for down-scattered Tc-99m counts and for radioactivity from Tl-201 gamma rays (135 and 167 keV) according to the following formulas[1]: $a = A - B\alpha$, $b = B - A\beta$ where a = corrected Tl-201 counts, A = total sample counts at 75 keV, α = Tc-99m standard at 75 keV/Tc-99m standard at 140 keV, b = corrected Tc-99m counts, B = total sample counts at 140 keV, and β = Tl-201 standard at 140 keV/Tl-201 standard at 75 keV.

Data processing and overlay technique: Tl-201 and Tc-99m tomograms were separately reconstructed according to the method used by Vogel et al.[14] Sixteen sections of nominal 0.8 cm intervals were generated. After reconstruction, images were viewed using a 15-step color scale. For dual isotope display, the Tc-99m images were background-subtracted to ensure that residual blood pool activity was just below the display limit. Then the images were inversely colored and overlaid on the normally colored Tl-201 images.

For sizing the infarction, each short-axis slice was subdivided into 8 segments. Relative size of the Tl-201 defects and the Tc-99m PYP accumulation was expressed as the number of segments involved. The results of 6 slices were averaged. Tc-99m PYP uptake ratio was assessed by calculating Tc-99m PYP target to blood pool ratios for the area of infarction and for myo-

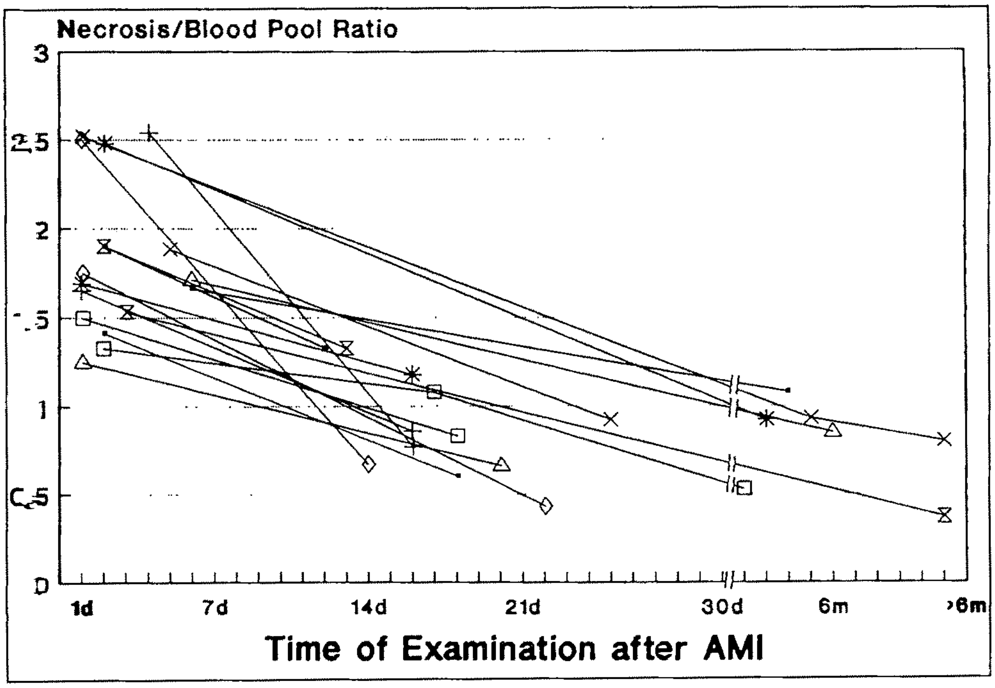

FIGURE 1. Time course of technetium-99m pyrophosphate accumulation in 17 patients with early imaging (within 7 days after acute myocardial infarction [AMI]) and follow-up examination (13 days to 4 years). Infarct to blood pool ratio in the latter scintigrams decreased in all cases.

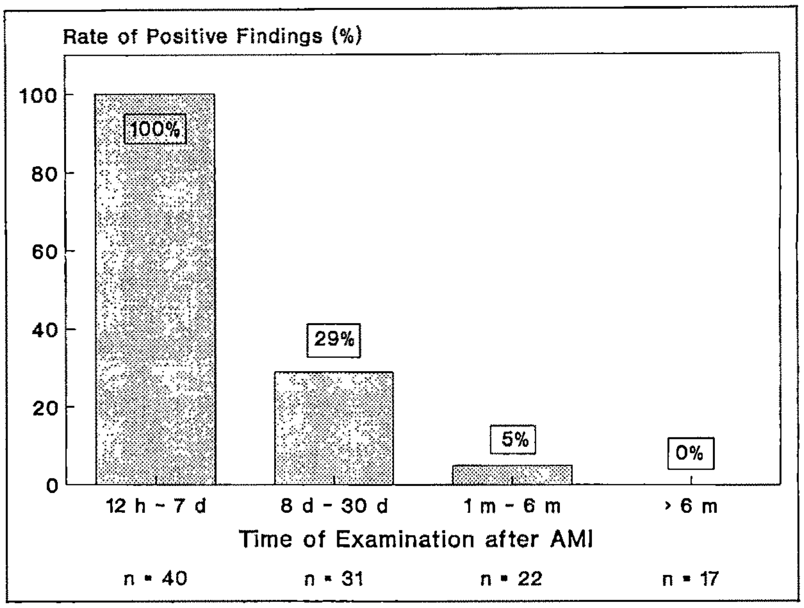

FIGURE 2. Positive rate (infarct to blood pool ratio >1.0) of technetium-99m pyrophosphate scintigraphy depending on the time of examination after acute myocardial infarction (AMI).

cardium with normal Tl-201 uptake, respectively. Tc-99m PYP uptake ratio >1.0 was considered abnormal if measured on ≥ 2 contiguous short-axis slices. Tl-201 defects had to be present on at least 2 contiguous short-axis slices as well.

Statistical analysis: Values reported are mean ± 1 standard deviation. Comparisons between groups were made with the Fisher's exact test. For multiple-comparison Scheffé's method was applied.

RESULTS

Scintigraphic findings in the four different groups: Table I summarizes the clinical and scintigraphic parameters. A perfusion defect on the Tl-201 tomograms was seen in all patients studied. The relative size of the perfusion defect did not differ between the 4 groups (groups A to D: 2.65 ± 1.55, 2.58 ± 1.11, 3.03 ± 1.72 and 2.51 ± 1.7 segments). Moreover, Tl-201 defect size was comparable in patients in group B with and without positive Tc-99m PYP accumulation (Tc-99m PYP+, 2.6 ± 1.8 segments; Tc-99m PYP−, 2.2 ± 1.6 segments). Tc-99m PYP uptake (Figure 2) was present in all 40 patients in group A (AMI within 7 days) (Figure 3), 9 of 31 patients in group B (7 to 30 days after AMI), 1 of 22 patients in group C (1 to 6 months after AMI), and no (0 of 17) patient in group D (>6

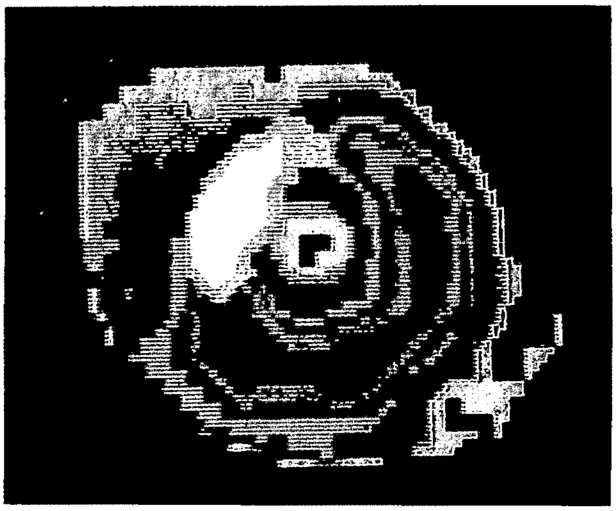

FIGURE 3. Acute transmural anteroseptal infarction. Short-axis cut of combined thallium-201/technetium-99m pyrophosphate tomography 3 days after acute myocardial infarction showing marked technetium-99m pyrophosphate uptake *(yellow and green)* in the anteroseptal wall. Normal thallium-201 accumulation is *red.*

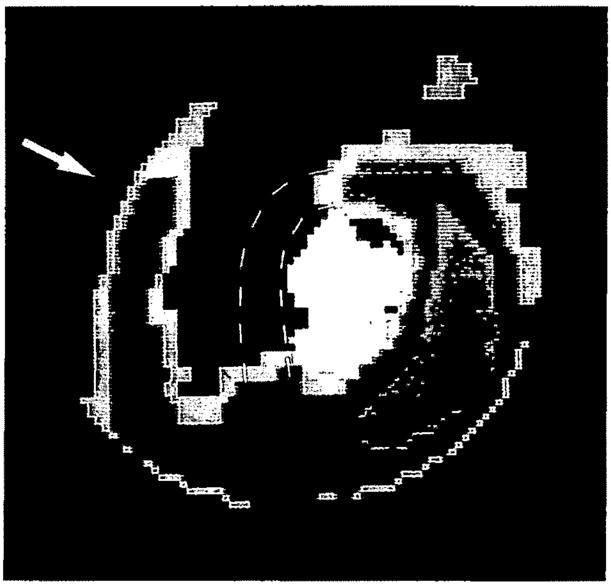

FIGURE 4. Anteroseptal infarction 8 months before scintigraphy. Short-axis cut of combined thallium-201/technetium-99m pyrophosphate tomography showing an evident region of reduced *(blue)* or even absent activity at the anteroseptal wall (silhuettes indicated by *dotted lines*). Furthermore, increased thallium-201 uptake was noted at right ventricular wall *(arrow)*. No pathologic technetium-99m pyrophosphate accumulation in the anteroseptal wall is seen. Remaining activity of left ventricular blood pool is *yellow.*

months after AMI) (Figure 4). Compared with group A, patients in Groups B, C and D had significantly lower Tc-99m PYP uptake ratio (1.54 ± 0.39 vs 0.89 ± 0.24, 0.80 ± 0.19, 0.76 ± 0.13; $p < 0.001$). However, despite a Tc-99m PYP uptake ratio <1 in the zone of the Tl-201 defect, this ratio was still higher in 47 of 70 studies of groups B, C and D compared with the Tc-99m PYP uptake ratio of myocardium with normal Tl-201 accumulation versus blood pool (0.81 ± 0.18 vs 0.53 ± 0.05; $p < 0.001$). In the same way, the size of areas with increased uptake of Tc-99m PYP above that of myocardium with normal Tl-201 accumulation also decreased (groups A to D: 2.73 ± 1.28, 0.90 ± 0.74, 0.84 ± 0.65 and 0.72 ± 0.50 segments). These findings were independent of the location of infarction in either the anterior or posterior wall.

Scintigraphic findings of the 17 patients with sequential examinations: In 17 patients, acute examination 2.8 ± 2.0 days after AMI was followed by an additional examination 1 week to 4 years later. All initial tomograms during the acute phase of AMI demonstrated a Tc-99m PYP uptake ratio >1. The Tc-99m PYP uptake ratio decreased in all patients at the follow-up examinations from 1.79 ± 0.4 to 0.84 ± 0.23 ($p < 0.01$) (Figure 1). Only 4 of these 17 patients exhibited a Tc-99m PYP uptake ratio of >1 on days 2, 13, 16 and 17, respectively, and 1 patient had it 4 months after AMI.

DISCUSSION

The present study demonstrates that in clinically stable patients without any evidence of persistent ischemia, (1) persistently positive Tc-99m PYP tomography is rarely seen >1 month after AMI (1 of 39; 3%), and (2) relative intensity as well as extension of Tc-99m PYP uptake decreases after 1 week post-AMI. Other investigators using the planar technique have also observed fading Tc-99m PYP accumulation on follow-up scintigrams.[5,6] In particular, low-grade diffuse uptake has been described in persistently positive scintigrams.[4,5,8,15–17] In agreement with these reports comparing myocardium with normal and decreased Tl-201 accumulation, we identified slightly increased Tc-99m PYP uptake (uptake ratio 0.5 to 1.0) compared with normal myocardium in 69% of the patients in groups B, C and D. Nevertheless, the tomographic technique classified 97% of these studies as normal.

Tc-99m PYP tomography has been shown to be a sensitive method for detecting AMI.[1–3] Even non-Q-wave infarction can be reliably detected, especially when performed by overlay technique with an anatomic marker such as either tomographic blood pool or Tl-201 scintigrams.[10,18] Although the 7-pinhole technique used for this study is apparently restricted by a limited depth resolution,[13,19] it has been shown to correctly identify and localize AMI.[11,18] However, the value of Tc-99m PYP infarction imaging has been questioned on several occasions because of persistently positive scintigrams.[5,7–9] Prior studies performed as planar scintigrams, reported persistently positive findings in up to 57% of the examinations within the first year after AMI[4,7,15] and prompted the search for more suitable markers for necrosis. Indium-111 antimyosin, a monoclonal antibody highly specific in delineating myocardial damage,[20] appeared most promising.[21–23] However, owing to the slow blood clearance of the tracer, imaging can be performed only 24 to 48 hours after injection.[21,24]

In contradistinction to indium-111 antimyosin scanning, Tc-99m PYP tomography of AMI is possible within the first hours.[25–27] Tc-99m PYP scintigraphy is particularly attractive for diagnosing acute myocardial necrosis when specificity is high. All previous studies reporting a low specificity of Tc-99m PYP scintigraphy were performed with the planar imaging technique.[5,7–9]

Several reasons may explain positive scintigrams not related to AMI. This has been reported for persistent Tc-99m PYP blood pool activity,[8,11,28] left mastectomy,[8,29] extensive AMI or ventricular aneurysm.[4,7,11,16] However, in the present study, infarct size determined by Tl-201 tomograms in group B patients with and without positive Tc-99m PYP uptake was not significantly different. Several factors may add up to an apparently positive planar scintigram, such as faint blood pool activity, slightly increased focal Tc-99m PYP uptake (uptake ratio 0.5 to 1.0), and physiologic accumulation in the bone. Tomographic imaging by dual radio isotope technique as a necessary prerequisite for supporting blood pool subtraction enables discrimination of adjacent structures and blood pool activity and therefore avoids misinterpretation.

Moreover, persistently positive Tc-99m PYP imaging can also be true positive, indicating ongoing myocardial necrosis.[4,30] According to clinicopathologic studies, a persistently positive scintigram was frequently correlated with myocytolytic degeneration and fibrosis,[31] acute[3,31,32] or recurrent ischemia[4,17] and chronic ischemic injury.[30,33] Persistent Tc-99m PYP uptake was found to predict cardiac death or impairment of left ventricular function.[6,30,33]

Study limitation: In this study we did not compare the planar and tomographic imaging techniques. Therefore, no conclusion can be drawn on the frequency of false-positive planar Tc-99m PYP scintigrams.

Conclusions: The present study shows that a positive Tc-99m PYP tomogram reliably indicates an acute myocardial necrosis and thus may be especially useful for detecting reinfarction. Tomographic imaging of Tc-

99m PYP accumulation may increase the specificity of this technique.

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Prognostic Significance of Silent Myocardial Ischemia in Variant Angina Pectoris

Raffaele Bugiardini, MD, Alberico Borghi, MD, Biagio Sassone, MD,
Andrea Pozzati, MD, and Paolo Puddu, MD

The present study investigates the prognostic significance of silent myocardial ischemia in variant angina. Forty-eight-hour Holter monitoring and coronary angiography were performed in 54 patients with transient ST elevation and no history of myocardial infarction admitted to the coronary care unit for worsening of symptoms. Coronary artery spasm was documented in most of these patients. Over the subsequent month, 20 patients (group 1) had a major coronary event (2 died, 6 had nonfatal myocardial infarction and 12 had urgent coronary revascularization), and the remaining 34 patients (group 2) had a good clinical outcome. From 2,578 hours of recording, 547 ischemic episodes were identified of which only 9% were associated with angina. The mean daily number of ST elevation in group 1 was similar to that in group 2 (4.8 ± 5.1 vs 4.1 ± 4.6; p = not significant). Conversely, the mean daily duration of such ischemic episodes was consistently greater in group 1 than in 2 (79 ± 36 vs 37 ± 25 minutes; $p < 0.005$). The occurrence of ≥1 long-lasting (≥10 minutes) episode of ST elevation was observed in 18 of 20 patients in group 1 (sensitivity 90%), but only in 4 of 34 in group 2 (specificity 88%). Significant coronary atherosclerosis (>50% stenoses) was found at angiography in 18 of 20 patients in group 1, and in 18 of 34 in group 2. Furthermore, morphologic analysis of coronary angiograms revealed the presence of a complex coronary stenosis (overhanging edges, irregular borders or intracoronary thrombus) in 16 of 20 patients in group 1, but only in 4 of 34 in group 2 ($p < 0.0005$). It is concluded that silent myocardial ischemia is an important predictor of unfavorable short-term clinical outcome due to high-risk (complex morphology) coronary stenoses in variant angina. Patients with coronary artery spasm but without plaque disruption have a benign prognosis.

(Am J Cardiol 1991;68:1581–1586)

The fact that patients with persistent angina at rest refractory to medical treatment form a high-risk group is well-established.[1-2] Other studies indicate that the elimination of symptoms alone may not ensure a favorable outcome[3] and demonstrate that persisting silent ischemia is associated with a greater occurrence of atherosclerotic plaque disruption and subsequent coronary events in unstable angina.[4,5] However, no agreement exists on the type of ST changes more frequently associated with an adverse short-term prognosis. The incidence of arrhythmias, acute myocardial infarction and consequent death has been found to be greater in patients with ST elevation (variant angina) than in those with ST depression, despite the observation of similar ventricular function and coronary anatomy.[6,7] These results were not confirmed by other reports that found that patients exhibiting either ST depression or elevation, or both, were similar with respect to frequency of multivessel disease, left main stenosis or unfavorable outcome.[8]

In this study we provide evidence that variant angina can be due to multiple causes, which implies variable susceptibility to coronary vasoconstriction, variable atherosclerosis involvement of coronary arteries, variable coronary stenosis morphology, and different acute risk for subsequent coronary events. Accordingly, selection of different subsets of patients could account for previous discrepancies.

METHODS

Patients: During a consecutive period of 24 months, 54 patients with variant angina and no history of myocardial infarction were admitted to the coronary care unit. Variant angina was defined as the occurrence of typical chest pain at rest associated with transient ST elevation without evidence of acute myocardial infarction (defined by typical changes on the electrocardiogram or in serum cardiac enzyme release [creatine-ki-

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nase >2 times normal, with MB fraction >6%], or both). Criteria for exclusion from the study were: age >75 years; noninterpretable electrocardiogram; adverse outcome due to concomitant nonmyocardial disease; and severe heart failure. Patients with severe heart failure were excluded owing to the following considerations: (1) An unpaired ejection fraction is predictive of unfavorable outcome in patients with unstable angina.[1] (2) In the setting of left ventricular dysfunction, the remaining viable contractile elements could be vulnerable to the cardiodepressant effects of calcium antagonists. This would have made it difficult to use a standard drug treatment in all patients. Furthermore, patients who developed an acute myocardial infarction in the first 24 hours were not enrolled in the study, because our modeling strategy was based on Holter recordings that at the present may give prognostic information only after 24-hour analysis.[4] All patients were initially treated with a standard medical regimen (intravenous nitroglycerin [10 to 60 μg/min], oral calcium antagonists [verapamil 240 to 360 mg/day], β blockers [propranolol 60 to 240 mg/day] and oral aspirin [325 mg/day]). Also, 0.5 mg of intravenous nitroglycerin or 5 mg of sublingual isosorbide dinitrate were administered as needed. None of the patients had bradycardia or ventricular dysfunction during medical therapy.

ST-segment monitoring: Forty-eight-hour ST-segment monitoring was begun 8 ± 7 hours after the qualifying episode of chest pain. We used a 2-channel Holter system (Applied Cardiac System 8300 frequency modulated recorders; frequency response 0.05 to 100 Hz). The 2 leads showing the most pronounced reversible ischemic changes on the initial qualifying 12-lead electrocardiogram were selected for analysis. Recordings were printed in a minielectrocardiogram format by a Telemed Saturn 3200 analyzer. Holter monitoring was interpreted by investigators unaware of the clinical data. Of the 54 patients, 34 had ST elevation and 20 had isoelectric ST segment on admission. Only episodes lasting ≥60 seconds and with ≥0.15 mV of ST-segment shift were considered for analytical purposes. All recordings were obtained while patients were resting in bed. Patients and attending nurses kept a careful diary of symptoms.

Coronary angiography: Selective coronary angiography was performed within 1 week of admission. Of the 54 patients 12 underwent urgent cardiac catheterization 2.3 ± 1.2 days after admission. The remaining patients underwent elective catheterization 6.6 ± 1.5 days after admission. The severity and morphology of coronary artery stenosis were observed in multiple views. Analysis of the end-diastolic cineframes was performed by 2 teams of investigators, each comprised of 2 observers experienced in angiographic interpretation and unaware of the clinical data. Differences were mediated by consensus. A stenosis ≥50% was considered significant. Complex angiographic morphology was defined as any significant asymmetric stenosis with irregular borders, overhanging edges or intraluminal thrombus. Correlation between electrocardiographic changes during angina and coronary anatomy at angiography has been described elsewhere.[9] When recognition of the ischemia-related stenosis was uncertain, the most severe narrowing of the artery was chosen for analysis. This applied only to 2 cases. None of the patients had stenosis <50% associated with complex coronary morphology. Accordingly, patients with narrowing <50% were grouped together and classified as having "normal or near normal arteries."

Hyperventilation or ergonovine testing was performed in 38 of the 54 patients. Coronary spasm was diagnosed as a transient coronary artery occlusion accompanied by evidence of transient ST-segment shifts ≥0.1 mV. It was relieved by sublingual or intravenous nitrates.

Unfavorable outcome: Unfavorable hospital outcome was defined as myocardial infarction, death, or need for urgent aortocoronary bypass or percutaneous transluminal coronary angioplasty. The decision to perform emergency revascularization was made according to protocol on the basis of the patient's symptomatic behavior.

Emergency revascularization required: (1) impending myocardial infarction (i.e., need for thrombolysis owing to the occurrence of prolonged (≥30 minutes) chest pain accompanied by ST elevation ≥0.1 mV unrelieved by 0.5 mg intravenous nitroglycerin, relief of symptoms and ST elevation after intravenous thrombolysis, and no evidence of significant enzyme release); (2) recurrent (≥3 times daily) chest pain with accompanying electrocardiographic changes of ischemia despite complete bed rest and medical regimen for ≥2 days after the first 24 hours in the coronary care unit; and (3) severe (stenosis ≥70%) coronary artery disease associated with one of the above findings.

Data analysis: We analyzed both quantitative and qualitative features. The former were expressed as mean ± standard deviation, and comparisons were obtained with Student's *t* test for unpaired data and with Mann-Whitney test when appropriate. The latter were expressed as percentages and were arranged in 2 × 2 contingency tables for statistical inference, and chi-square with Yates correction method was used. The Fisher exact test was also used when appropriate. Kaplan-Meyer analysis was used to examine the time-dependent cumulative probabilities of the outcomes, and differences were tested by the method of Breslow. A p value <0.05 was considered statistically significant.

TABLE I Clinical and Angiographic Features of 54 Patients with Variant Angina, and Relation to Prognosis

	Clinical Outcome		
	Unfavorable (group 1: n = 20)	Favorable (group 2: n = 34)	p Value
Age (yrs)	59	61	NS
Men/women	15/5	28/6	NS
Diabetes mellitus (%)	2 (10)	2 (6)	NS
Previous angina (%)	11 (55)	16 (47)	NS
In-hospital therapy			
Intravenous nitroglycerin (μg/min)	37 ± 16	36 ± 24	NS
Propranolol (mg/day)	116 ± 40	124 ± 27	NS
Verapamil (mg/day)	293 ± 68	268 ± 72	NS
Aspirin (mg/day)	325	325	NS
Number of coronary arteries narrowed ≥ 50% in diameter			
0-Vessel CAD (%)	2 (10)	16 (47)	<0.005
1-Vessel CAD (%)	10 (50)	6 (18)	<0.05
2-Vessel CAD (%)	2 (10)	12 (35)	<0.05
3-Vessel CAD (%)	6 (30)	0 (0)	<0.005
Mean IRA stenosis (%)	92 ± 6	78 ± 20	<0.005
Ejection fraction (mean %)	61 ± 11	63 ± 13	NS

CAD = coronary artery disease; IRA = ischemia-related artery; NS = not significant.

RESULTS

During hospitalization, 20 patients (group 1) had a major coronary event; 6 had nonfatal myocardial infarction, 2 died and 12 underwent urgent coronary revascularization (8 angioplasties and 4 aortocoronary bypass operations). The remaining 34 patients (group 2) had a good clinical outcome. Angiographic characteristics of the 2 study groups as well as details of antianginal therapy during Holter monitoring are listed in Table I. After discharge, coronary angioplasty and bypass procedures were performed in an additional 3 patients. Elective interventions were not considered as unfavorable outcome, because their indications were mainly owing to persistence of symptoms of chronic stable angina, as well as to severe coronary artery disease.

Holter electrocardiographic monitoring: From 2,578 hours of recording, 547 ischemic episodes were identified of which only 9% were associated with angina. Most patients (93%) had both symptomatic and asymptomatic ST shifts. The remaining 7% of patients had silent ischemia exclusively. Mean daily number of ST elevation per patient in group 1 was similar to that in group 2 (4.8 ± 5.1 vs 4.1 ± 4.6). Patients had few episodes of ST depression (76). Mean daily number of ST depression per patient in group 1 was not significantly different from that in group 2 (0.8 ± 2.1 vs 0.7 ± 1.7). Conversely, the mean duration per 24 hours (Figure 1) of the ischemic episodes (including both ST elevation and depression) was consistently greater in group 1 than in 2 (79 ± 36 vs 37 ± 25 minutes; p <0.005). Kaplan-Meyer analysis demonstrated a significantly greater cumulative probability of subsequent coronary events in patients with transient myocardial ischemia ≥60 minutes/24 hours (p <0.01). This is in agreement with previous studies.[4,5,8] Ischemia ≥60 minutes occurred in 14 of 20 patients in group 1 (sensitivity 70%) and in 6 of 34 in group 2 (specificity 82%). Kaplan-Meyer analysis also demonstrated that patients with episodes of transient ST elevation ≥10 minutes had a significantly greater cumulative probability of infarction or revascularization (p <0.0003; Figure 2). Recordings of ≥1 ST-elevation episode ranging from

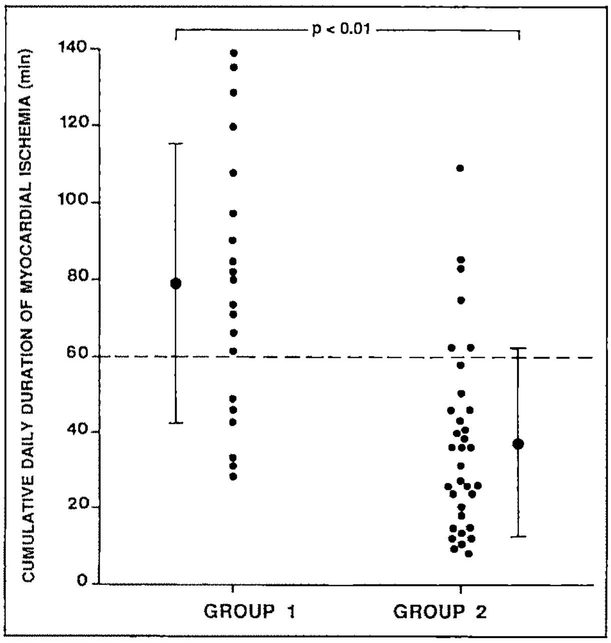

FIGURE 1. Relation between cumulative daily duration of ischemia (including both ST elevation and depression) and prognosis. Ischemia ≥60 minutes/24 hours was able to identify the majority of patients having subsequent coronary events (group 1). Few patients with favorable outcome showed similar findings (group 2).

10 to 30 minutes were observed in 18 of 20 patients in group 1 (sensitivity 90%), but only in 4 of 34 in group 2 (specificity 88%).

Coronary angiography: Quantitative and qualitative analyses of coronary angiograms were performed in all 54 patients. Coronary lesions were morphologically classified using the criteria of Ambrose et al.[9] Significant coronary atherosclerosis (≥50% stenosis) was seen in 18 of the 20 patients in group 1, and in 18 of the 34 in group 2 ($p < 0.005$). Mean coronary narrowing was 92% in the 18 patients in group 1 (range 80 to 99%), and 78% in the 18 atherosclerotic patients in group 2 (range 50 to 99%). Morphologic analysis of coronary angiograms revealed the presence of a complex coronary stenosis in 16 of the 18 atherosclerotic patients in group 1, but only in 4 of the 18 in group 2 ($p < 0.0005$).

Coronary vasospasm: Of the 38 provocative tests performed in the overall study group 34 were positive. No significant difference was found between the groups. Spontaneous or induced coronary vasospasm was seen in 10 of the 12 patients in group 1, and in 24 of the 26 in group 2.

Clinical outcome: We recognized that the basis for indicating urgent coronary revascularization has often included a subjective component (i.e., the rate of occurrence of chest pain); therefore we also analyzed the results of Holter monitoring using only the following hard end points: urgent revascularization owing to impending myocardial infarction (6 patients); nonfatal myocardial infarction (6); and death (2). Patients with these end points had a significantly longer duration of ST shifts than did patients without these end points (69 ± 11 vs 46 ± 20 minutes; $p < 0.01$). All of these patients had ≥1 episode of transient ST elevation ≥10 minutes, and 10 of 14 had a cumulative duration of myocardial ischemia ≥60 minutes/24 hours. Clinical outcome and symptomatic behavior of patients in group 1 are listed in Table II. A sample of 10 patients in group 2 is shown for comparison (Table III). The majority of patients in group 1 had symptoms that were not indicative of the occurrence of subsequent coronary events.

DISCUSSION

Since the advent of coronary angiography, evidence has been accumulated that variant angina (i.e., chest pain associated with ST elevation) may develop in patients with normal coronary arteries or with atherosclerotic changes involving 1, 2 or 3 vessels. Many studies combine cases with and without coronary artery disease, presenting jointly their clinical features. This could generate misleading and apparent discrepancies between different trials.[6–8] Our study demonstrates that patients with variant angina do indeed differ in natural history and clinical outcome depending on the presence of atherosclerosis and plaque rupture, which appears to be a random event in the progression of coronary atherosclerosis. This study also demonstrates that electrocardiographic manifestations can distinguish those patients with high risk of subsequent coronary events from those with a benign prognosis.

Relation between clinical outcome, coronary spasm and atherosclerosis: It is firmly established that coronary artery spasm is quite often responsible for the occurrence of ischemia in patients with variant angina.[10]

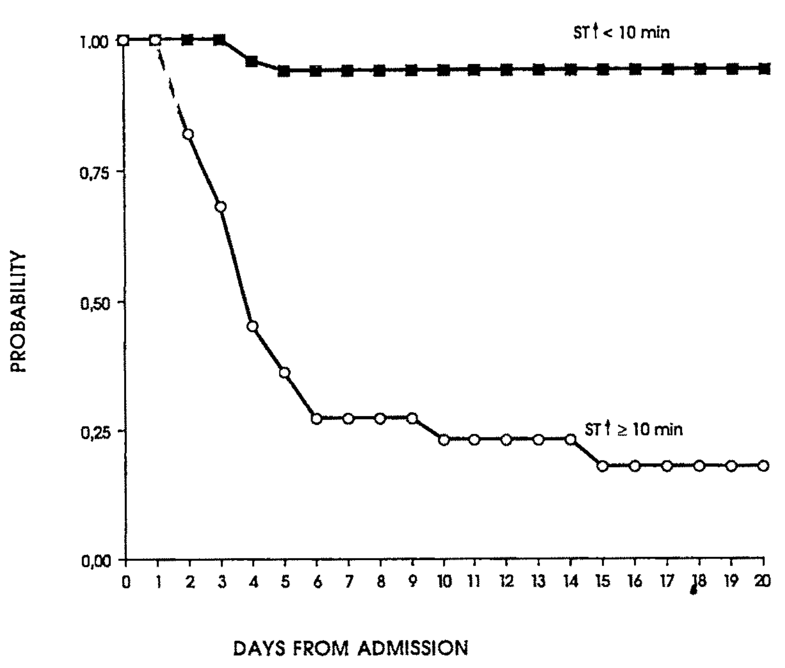

FIGURE 2. Kaplan-Meyer curves comparing cumulative probabilities of not having death, myocardial infarction or urgent revascularization during a period of 20 days for patients presenting with or without ≥1 prolonged (≥10 minutes) episode of ST elevation, as detected by 24-hour continuous electrocardiographic monitoring ($p < 0.0003$).

TABLE II Clinical Outcome and Symptomatic Behavior of Patients with Variant Angina Having Subsequent Coronary Events

Pt.	End Point	Days Before Occurrence	Max. No. of Anginal Attacks/Day	No. of Days with Angina	TL	CK	TMI/24 hrs (min)	≥1 Episode ≥10 min ST ↑
1	Death	15	2	1	–	0	65	+
2	Death	6	3	3	+	+	80	+
3	AMI	4	0	0	+	+	46	+
4	AMI	10	3	2	–	+	52	+
5	AMI	3	1	1	+	+	32	+
6	AMI	2	2	1	+	+	43	+
7	AMI	2	2	1	+	+	62	+
8	AMI	2	3	2	+	+	71	+
9	CABG	4	3	3	+	0	84	+
10	CABG	5	4	2	+	0	73	+
11	CABG	3	3	2	+	0	81	+
12	CABG	4	1	2	+	0	90	+
13	PTCA	2	2	1	+	0	120	+
14	PTCA	4	1	2	+	0	97	+
15	PTCA	3	3	3	–	0	129	+
16	PTCA	5	4	3	–	0	108	+
17	PTCA	4	4	3	–	0	146	0
18	PTCA	6	4	3	–	0	48	+
19	PTCA	4	3	4	–	0	31	+
20	PTCA	5	3	5	–	0	108	0

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CK = significant creatine-kinase release; Max. = maximal; PTCA = percutaneous transluminal coronary angioplasty; ST ↑ = ST elevation; TL = intravenous thrombolysis; TMI = cumulative duration of transient myocardial ischemia.

This is confirmed by the present study. Indeed, angiographic evidence of spasm showing complete occlusion of the great epicardial vessels was largely documented in our patients whether they had adverse (83%) or benign (92%) clinical outcome (groups 1 and 2, respectively). Because only 2 of the 20 patients in group 1 had normal or near normal coronary arteries we agree with previous reports that spasm of nondiseased vessels can seldom evolve toward myocardial infarction.[7,11] Spasm, however, has been postulated to have a prognostic role in patients with significant coronary artery disease.[12] It may increase the degree of obstruction already present from anatomic lesion, which may cause a more frequent and sustained cessation of flow[13] leading to intracoronary thrombosis and myocardial infarction. Although plausible, this hypothesis does not seem to be supported by our data; 36 patients had significant atherosclerosis, but only 18 had subsequent coronary events (group 1).

It seems more conceivable, therefore, that other factors rather than a simple combination of spasm and atherosclerosis may severely interfere with coronary flow leading to prolonged coronary occlusion and myocardial infarction. Accordingly, the most significant difference between patients with adverse and favorable clinical outcomes was the frequency of the angiographic documentation of complex coronary morphology, which was the rule in the former (80%) and the exception (12%) in the latter. This supports the opinion that progression from anginal syndromes (whatever are the causes) to myocardial infarction has a common underlying pathologic basis (ruptured atherosclerotic plaque and acute thrombus formation).[14,15]

TABLE III Symptomatic Behavior of Patients with Variant Angina Having Subsequent Favorable Clinical Outcome (sample of 10 representative cases)

Patient	Max. No. of Anginal Attacks/Day	No. of Days with Angina	TMI/24 hrs (min)	≥1 Episode ≥10 min ST ↑
1	2	3	58	0
2	3	2	49	0
3	3	2	20	0
4	3	4	43	0
5	5	1	14	0
6	3	3	24	0
7	2	1	14	0
8	2	3	85	0
9	4	3	25	0
10	2	2	38	+

Abbreviation as in Table II.

Electrocardiographic predictors of adverse clinical outcome: Numerous studies have demonstrated that detection of silent ischemia during continuous electrocardiographic monitoring confers adverse clinical outcome and poor survival to patients with various anginal syndromes.[3,4,16,17] The prevalence of silent ischemia (91% of the episodes in our series) and its association with the increased rate of subsequent coronary events extend these observations to patients with variant angina. In our study, the risk of myocardial infarction and cardiac death was more related to the longer duration than to the mere presence of silent ischemia. Among the 20 patients in group 1, 14 were identified by a duration of ST shifts ≥60 minutes/24 hours on admission (sensibility 70%), and 18 by the occurrence of long lasting (≥10 minutes) episodes of transient ST elevation (sensibility 90%). The exact reason for the greater method sensitivity of the use of ST elevation ≥ 10 minutes/episode than that of the cumulative duration of ST shifts ≥ 60 minutes/24 hours is not clear. The relatively small number of patients eligible for this study may account for such a difference. Alternatively, it can be thought that the anatomical substrate underlying ischemia rather than ischemia itself is the real link with prognosis. For example, repeated, short (<10 minutes) episodes of myocardial ischemia due to "pure" coronary spasm (i.e., chronic hyperreactivity of angiographically normal or smooth, regular stenotic segments in the absence of intracoronary thrombosis) may lead to a cumulative duration of ischemia ≥ 60 minutes/24 hours without causing subsequent coronary events. In contrast, the presence of an exaggerated segmental vasoreactivity capable of leading to intense, persisting (≥ 10 minutes) vessel occlusion could be more frequent in patients presenting with acute coronary syndromes due to atherosclerotic plaque disruption with increased risk of intracoronary thrombosis and myocardial infarction. This hypothesis is strongly supported by the postmortem observation of contraction bands found in the smooth muscle surrounding plaques in patients who died with acute infarction or unstable angina.[18]

Clinical implications: Chest pain associated with ST elevation is often referred to as "variant angina." We have retained this term because it identifies patients with segmental coronary hyperreactivity to vasoconstrictor stimuli. However, variant angina occurring during plaque disruption appears to represent merely a more serious than average form of unstable angina. Conversely, variant angina due to spasm of angiographically normal vessels or arteries with smooth coronary stenosis appears to have a relatively benign prognosis. Difference in clinical presentation of pain provides insufficient information to withhold emergency invasive studies in most patients who do not need them (Tables II and III). In contrast, electrocardiographic data on silent ischemia may help to individuate the nature of the underlying coronary lesion and related prognosis, and may provide a modelling strategy for ongoing emergency coronary angiography and revascularization.

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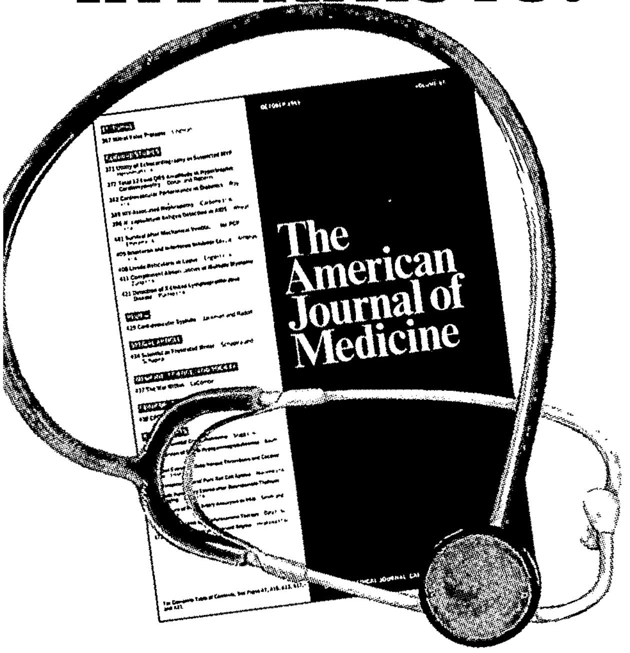

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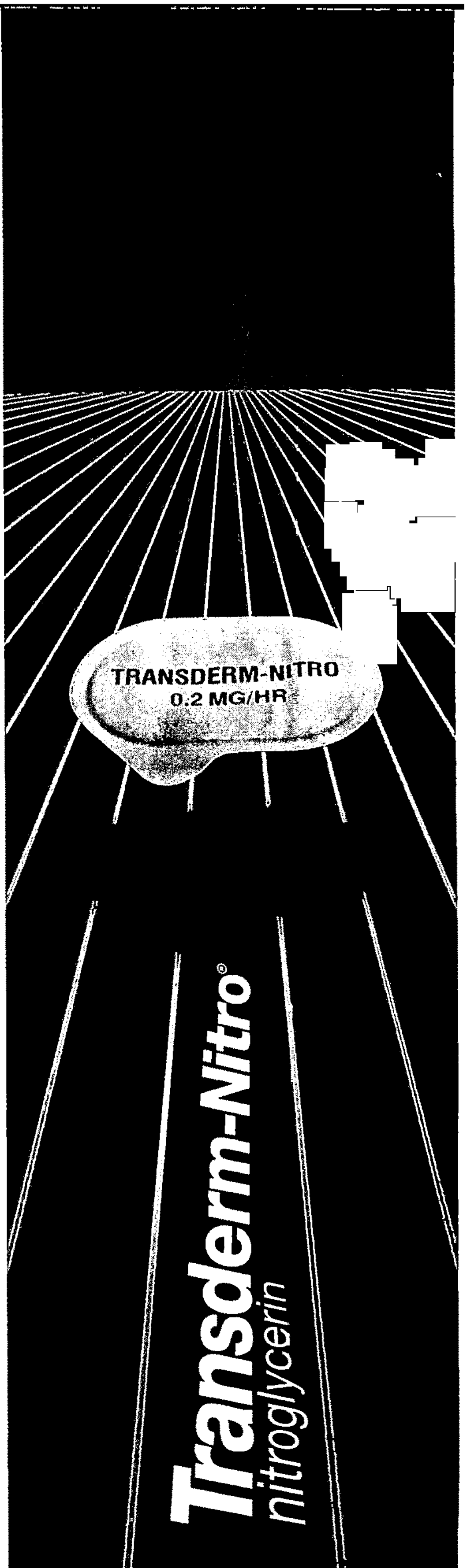

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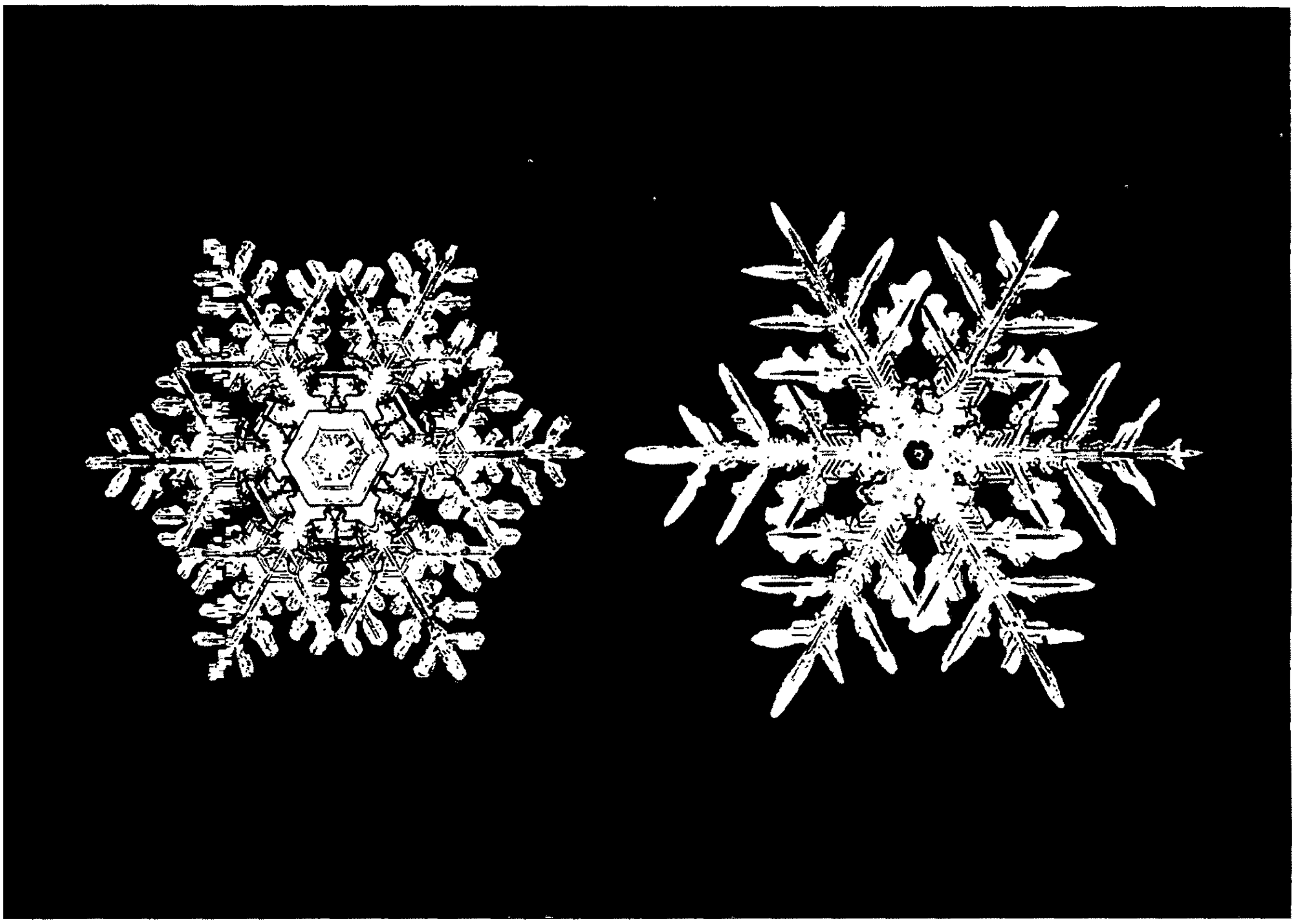

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Take the case of two patients suffering from hypertension. Both under the care of the same physician, who prescribes the same medication for each. One patient responds to the medication while the other reports unpleasant side-effects. Thanks to the diversity of drugs available to treat this illness, the doctor is able to prescribe another medicine that works without the side effects.

To maintain the high standards of quality care, and because some drugs work better than others on different people, it is essential to have this diversity.

America's research-based pharmaceutical companies are committed to providing a wide range of drugs of the highest quality to serve the public. Why? Because the public is made up of different people requiring different treatment—even when they suffer from the same illness.

Pharmaceutical Manufacturers Association

IF A NEW MEDICINE CAN HELP, WE'RE WORKING ON IT.

Felodipine (Once Daily) Versus Nifedipine (Four Times Daily) for Prinzmetal's Angina Pectoris

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In 30 consecutive patients with Prinzmetal's angina pectoris, the antiischemic effect of felodipine, a new long-acting vasoselective calcium antagonist, administered at doses of 10 and 20 mg once daily was compared with that of the well-established therapeutic regimen with nifedipine administered at a dose of 20 mg 4 times daily. Twenty-four-hour Holter monitoring was performed during a 2-day placebo run-in and at the end of each of 3 consecutive 6-day periods during which the 3 active treatments were administered in randomized sequence. Three patients withdrew, whereas 27 completed the study. The therapeutic regimens tested proved to be similarly effective; primary end points (ischemic episodes recorded by Holter monitoring, and anginal attacks reported on diary cards) occurred in 5 patients (19%) during nifedipine treatment, and in 7 (26%) and 3 (11%) during felodipine treatment with 10 and 20 mg, respectively (p = not significant). The distribution of residual ischemic episodes demonstrated that treatment with felodipine once daily provides 24-hour antiischemic protection. Twenty-six patients were followed up with 20 mg of felodipine once daily for a mean of 6 ± 5 months, and 21 of them (81%) remained free of symptoms and Holter-recorded ischemic attacks. It is concluded that for Prinzmetal's angina pectoris, 24-hour antiischemic protection may be achieved with administration of felodipine once daily. The availability of a simplified therapeutic approach may constitute a real advantage in terms of patient compliance and improving the quality of life.

(Am J Cardiol 1991;68:1587–1592)

Calcium antagonists have proved to be effective in the treatment of Prinzmetal's angina pectoris. Nifedipine,[1-4] verapamil[5-7] and diltiazem[8-11] have been shown to have comparable efficacy in reducing the occurrence of angina, nitroglycerin consumption and ST-segment changes by Holter monitoring, both acutely and during chronic treatment. A recent study demonstrated that calcium antagonists improve prognosis in this syndrome by reducing the occurrence of myocardial infarction and mortality.[12] Some recently developed calcium antagonists have promising pharmacological characteristics for the treatment of Prinzmetal's angina, such as higher vascular selectivity and longer duration of action, which would allow once-daily administration. Although spontaneous remission may occur with Prinzmetal's angina, continuous treatment is generally required[13,14]; therefore, the availability of a once-daily treatment may constitute a real advantage in terms of patient compliance and improving the quality of life. This study was performed to compare the short-term therapeutic efficacy of the dihydropyridine calcium antagonist felodipine, administered once daily, with that of its parent compound nifedipine administered at the well-established dose of 20 mg 4 times daily.[15] The long-term efficacy and safety of felodipine was also evaluated.

METHODS

Patient selection: From August 1988 to October 1990, 30 consecutive patients were identified during hospitalization as having Prinzmetal's variant angina pectoris and were enrolled in this study. All patients had a typical history of chest pain at rest promptly relieved by nitroglycerin, an objective demonstration of transient ST-segment elevation ≥0.1 mV on a standard 12-lead electrocardiogram during spontaneous attacks, and a positive response to ergonovine or hyperventilation test performed according to methods that have been extensively described elsewhere.[14,16] None of the patients had any evidence of myocardial necrosis after either spontaneous or induced ischemic episodes. Exclusion criteria included: previous coronary artery bypass or angioplasty; myocardial infarction within the preceding 6 months; congestive heart failure; systolic blood pressure <110 mmHg; electrocardiographic abnormalities that would interfere with the interpretation of ST-

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segment changes; known allergy to dihydropyridines; and serious concomitant illnesses. Written informed consent was obtained, and the study protocol and consent form were approved by the institutional review board.

Study design: The study was a double-blind comparison (with the exception of the first 6 patients) of the short-term efficacy of felodipine extended-release tablets (10 and 20 mg once daily) with nifedipine capsules (20 mg 4 times daily) administered for 6 days each in randomized sequence, according to a 3 × 3 Latin square design. During run-in and the short-term study, blinding was maintained according to the double-dummy technique; patients were administered 2 felodipine tablets (10 mg) or placebo and 4 nifedipine capsules (20 mg) or placebo. Nifedipine was administered at 6.00 A.M. and 12.00 A.M., and at 6.00 P.M. and 12.00 P.M., whereas felodipine was administered at 8.00 A.M. After completing this short-term protocol, patients began an open-label phase during which they received felodipine extended release tablets (20 mg) once daily. No concomitant prophylactic antianginal treatment was allowed during the entire study.

Short-term study: After a 48-hour gradual withdrawal of previous antianginal medication patients began a 2-day placebo run-in period during which only sublingual nitroglycerin was administered to relieve anginal attacks. To prevent any possible risk while on placebo medication, patients were hospitalized in the coronary care unit under continuous electrocardiographic monitoring; the run-in period could be shortened, and the active double-blind treatment begun, if ischemia were severe enough to warrant the administration of active medication. Twenty-four-hour Holter monitoring was performed on the last day of the run-in period, and patients were then randomized to 1 of the 3 treatment sequences. On the last day of each phase of the active crossover study, 24-hour Holter monitoring was repeated. During the study, patients kept a record by means of diary cards of the number, duration and severity of anginal attacks, and the number of sublingual nitroglycerin tablets consumed. Blood samples for determination of plasma concentrations of nifedipine and felodipine were obtained by standardized venipuncture 2 to 3 hours after drug intake on the 5th day of each period and were immediately centrifuged. Plasma was immediately stored at −20°C in opaque tubes and was kept frozen until analysis.

Long-term follow-up: During long-term follow-up, felodipine (20 mg) was administered once daily at 8 A.M. Patients were examined every 2 months, and 24-hour Holter monitoring was repeated at each examination. Diary cards to record anginal symptoms, nitroglycerin consumption and side effects were kept by the patients as described previously. A reduction in dosage to 10 mg of felodipine was allowed if the patient had no symptoms and signs of myocardial ischemia for the previous 6 months. In the case of persisting anginal attacks or ischemic episodes, the investigators could administer nitrates or another calcium antagonist to patients. Patients undergoing coronary revascularization were withdrawn from the study; however, their maximal follow-up time was computed, and they were considered to have concluded the study.

Study end points: The primary end points of the study were ischemic episodes recorded on Holter monitoring and anginal attacks reported in the diary cards during active treatment. A secondary end point of the study was the circadian distribution of residual ST-segment changes on Holter monitoring as a measure of the 24-hour antiischemic activity of the drug regimens.

Holter monitoring: Ambulatory electrocardiographic monitoring was performed using a Delmar Avionics Electrocardiocorder model 445 with a frequency response of 0.05 to 100 Hz, thereby meeting the American Heart Association specifications for heart rate and ST-segment changes. The leads showing the most evident electrocardiographic changes during spontaneous attacks were monitored. Leads with abnormal waves or significant ST-segment shifts at rest were avoided, and control recordings were obtained for each patient in the supine, prone, standing and sitting positions to ensure that the ST-segment was not affected by body position. The system was calibrated before and after each placement. Patients were instructed to press the "event button" on the recorder if they experienced chest pain, and to report episodes of chest pain and consumption of nitroglycerin on the diary card. Tapes were analyzed at 60 times the real time under continuous visual inspection, and an episode of transient ischemia was defined as ≥1 mm ST-segment elevation or depression occurring 80 ms after the J point, lasting for ≥1 minute and separated from other episodes by ≥1 minute. When a significant ST-segment change was noted on the monitor, the episode was recorded on electrocardiographic paper at 25 mm/s.

Coronary arteriography: Selective coronary arteriography was performed in multiple views using the Sones or Judkins techniques after premedication with 10 mg of diazepam. Narrowings of ≥70% were considered to be significant coronary stenoses. When a lesion was noted, the vessel was filmed again after intracoronary administration of nitroglycerin. Patients were classified as having 1-, 2- or 3-vessel disease according to the number of vessels with significant coronary stenoses.

Statistical analysis: The proportion of patients with either Holter-recorded ischemic episodes or anginal attacks during the randomized treatments were compared by means of the McNemar test, with a 2-tailed p value <0.05 considered statistically significant. Possible time effects were investigated by means of a "per period" analysis of the data. Continuous data are presented as mean ± standard deviation.

RESULTS

Patient characteristics: The clinical and angiographic characteristics of the 30 patients enrolled in the study are listed in Table I. No patient withdrew during the run-in period. After randomization, 1 patient could not tolerate any of the 3 treatments owing to dizziness and hypotension during the first day of administration of each treatment. One patient with history of gastritis experienced melena after occasional aspirin intake and was withdrawn from the study during the second period of treatment. One patient with transient ST-segment elevations in the anterior leads experienced a prolonged episode of chest pain associated with ST-segment elevation in the same leads and accompanied by an increase in the level of creatine kinase. This patient was classified as having a non-Q-wave myocardial infarction and was withdrawn from the study. This occurred during the first treatment period while the patient was receiving nifedipine. Therefore, the data reported in the present study were derived from the remaining 27 patients who completed all 3 periods of the short-term protocol. Compliance with the therapeutic regimen (as judged by the returned tablet count) was 96 ± 10% during the short-term study, and 89 ± 9% during the long-term study. During the short-term study, mean drug plasma concentrations were 125 ± 98 nmol/liter during nifedipine treatment, 14 ± 12 nmol/liter during felodipine (10 mg), and 14 ± 8 nmol/liter during felodipine (20 mg).

TABLE I Clinical and Angiographic Characteristics of the 30 Patients Enrolled in the Study

Sex (men/women)	28/2
Age (yrs)	54 ± 7
Previous myocardial infarction	5 (17%)
History of hypertension	9 (30%)
History of smoking	25 (83%)
Hypercholesterolemia	16 (53%)
Diabetes	3 (10%)
Duration of angina (mos)	6 ± 11
Time between inclusion and last pain (days)	5 ± 7
Mean weekly episodes of angina before enrollment	4.1 ± 4.5
History of effort angina	10 (33%)
No. of pts. who underwent angiography	28*
Normal coronary arteries	7 (25%)
Nonsignificant coronary stenoses (<70%)	5 (17%)
1-vessel disease (>70%)	13 (47%)
2-vessel disease (>70%)	3 (11%)

*Two patients refused coronary angiography.

Short-term study: A dramatic reduction in ST-segment changes, anginal symptoms and nitroglycerin consumption was observed after the initiation of the active medications irrespective of the drug administered (Table II). A complete absence of signs and symptoms was observed in 22 patients during period 1, in 23 during period 2, and in 21 during period 3. The "per treatment" analysis irrespective of the sequence of administration showed an equal number of patients with residual ischemic events and symptoms with all 3 randomized drugs (Table III). During the run-in period, ischemic ST-segment changes recorded by Holter monitoring were distributed throughout the 24 hours with a preferential clustering between 1:00 and 6:00 A.M. (Figure 1). There was no correlation between the occurrence of residual ischemic episodes observed during all 3 active treatments and the time from last drug administration (Figure 1). Side effects were mild and infrequent. During the placebo run-in period, no patient reported any side effect; 1 reported flushing during all 3

TABLE II Time Course of Ischemic Episodes, Anginal Attacks and Nitroglycerin Consumption During the Short-Term Study Irrespective of the Randomized Treatments

	Run-In (27 pts.)	Period 1 (27 pts.)	Period 2 (27 pts.)	Period 3 (27 pts.)
No. of pts. with ischemic episodes or anginal attacks	22	5	4	6
24-hour Holter				
No. of pts. with ischemic episodes	19	3	2	3
Total no. of ischemic episodes	122	8	3	2
Asymptomatic	80	7	1	1
Symptomatic	42	1	2	1
Diary cards				
No. of pts. with anginal attacks	20	4	4	5
Total no. of anginal attacks	56	13	14	9
Nitroglycerin consumption	25	3	10	1
No. of days of observation	46	152	157	163

No significant differences were observed among the 3 periods.

TABLE III Ischemic Episodes, Anginal Attacks and Nitroglycerin Consumption During the Short-Term Study Irrespective of the Sequence of Administration

		Felodipine	
	Nifedipine (27 pts.)	10 mg (27 pts.)	20 mg (27 pts.)
No. of pts. with ischemic episodes or anginal attacks	5	7	3
24-hour Holter			
No. of patients with ischemic episodes	3	3	2
Total no. of ischemic episodes	7	4	2
Asymptomatic	6	1	2
Symptomatic	1	3	0
Diary cards			
No. of pts. with anginal attacks	4	6	3
Total no. of anginal attacks	13	16	7
Nitroglycerin consumption	2	12	0
No. of days of observation	162	148	162

No significant differences were observed among the 3 treatment groups.

treatments, and another reported flushing and gastralgia while receiving felodipine (20 mg).

Long-term follow-up: Twenty-six of the 27 patients completing the short-term study were followed up with felodipine for a period of 4 days to 16 months (mean 6 ± 5 months). The remaining patient was excluded because he was resident in an area too far away from our institution for follow-up to be possible. In all, 73 examinations were performed, and 1,440 hours of Holter monitoring were obtained. During this period, 21 pa-

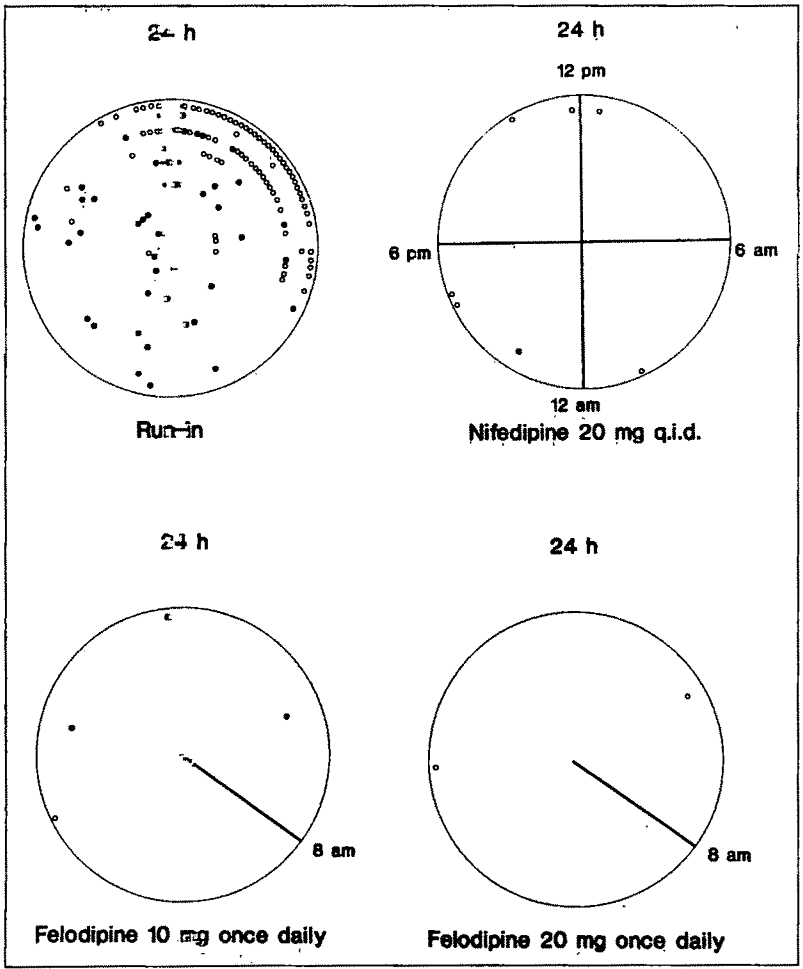

FIGURE 1. Twenty-four-hour distribution of symptomatic *(black circles)* and asymptomatic *(white circles)* ischemic episodes on Holter monitoring during run-in, 20 mg of nifedipine 4 times daily (q.i.d.), and 10 and 20 mg of felodipine once daily. Each *panel* represents a 24-hour clock; times of drug administration are represented by *radii*.

tients were free of symptoms and ischemic ST-changes on Holter monitoring. Two of these patients were withdrawn because of the development of ankle edema. The dosage of felodipine was reduced to 10 mg once daily in 12 patients who achieved a complete response for >6 months; no patient had anginal symptoms or electrocardiographic ischemia after dose reduction. Among 5 patients who did not achieve remission, 4 reported anginal attacks, and ischemia was detected during Holter monitoring in 4 (2 had both painful and painless episodes, 1 had only painless, and 1 had only painful). Nitrates or another calcium antagonist were administered to 3 patients; the other 2 who had significant coronary artery disease underwent coronary angioplasty.

DISCUSSION

Coronary artery spasm has been demonstrated as the pathogenetic mechanism of Prinzmetal's angina.[17,18] Therefore, the therapeutic approach to this syndrome has been directed at preventing the occurrence of coronary spasm. Calcium antagonists that reduce the vascular smooth muscle cell contractility proved extremely effective in controlling symptoms and electrocardiographic signs of ischemia in these patients.[1-11] In a previous study, we demonstrated the effectiveness of felodipine in preventing hyperventilation-induced coronary spasm in patients with Prinzmetal's angina.[19] Because felodipine is a long-acting calcium antagonist that has been shown to have 24-hour effectiveness as an antihypertensive agent[20,21] we decided to test its clinical efficacy as a once-daily antiischemic treatment for Prinzmetal's angina. Before inclusion in this study, all patients reported frequent anginal attacks, had a positive response to provocative tests and had ST-segment elevation on electrocardiogram during spontaneous attacks. Nineteen patients also showed ischemic ST-segment changes on Holter monitoring, and 20 reported anginal attacks during the run-in period preceding the study. The initiation of treatment with the calcium antagonist produced a prompt, dramatic reduction in the frequency of anginal attacks, nitroglycerin consumption and ischemic changes on Holter monitoring. The therapeutic regimens tested in this study proved to be similarly effective and tolerated; no difference was detected between either nifedipine and felodipine or felodipine at 2 different dosages. Analysis of the 24-hour distribution of residual ischemic episodes demonstrated that treatment with felodipine once daily ensures 24-hour antiischemic protection. Spontaneous remission appears to be a frequent event in Prinzmetal's angina,[13,14] and thus the absence of a placebo control may be considered as a limitation of the present study. However, the promptness and completeness of remission observed during all 3 periods of active treatment makes it unlikely that there was a spontaneous remission of the disease. Moreover, in view of the fact that calcium antagonists have been shown to improve prognosis in Prinzmetal's angina[12] and that cardiac deaths and nonfatal myocardial infarctions occur mostly before hospital discharge or within the first few months after hospitalization[22-25] we considered it unethical to conduct a placebo-controlled study. An active-controlled study is more appropriate to test the efficacy of the new dihydropyridine calcium antagonist felodipine for Prinzmetal's angina, and consequently it was compared with its parent compound nifedipine administered at a well-established dosage in accordance with previous reports on this syndrome.[15] Owing to the high antiischemic efficacy of calcium antagonists in Prinzmetal's angina and to the relative rarity of this disease, the sample size required to reach a reasonably high power to exclude a statistically significant difference in efficacy between 2 active calcium antagonists would require an exceedingly long period of time for patient enrollment, even for a specialized institution like ours. As a matter of fact, the 30 consecutive patients reported in this study constitute the entire number of patients with Prinzmetal's angina seen in our department during >2 years. However, our study allowed us to exclude, with a power of 0.8 and a type 1 error of 0.05, a difference between the least and the most effective treatment >21% based on the measurement of efficacy as a binary outcome. The long-term effectiveness of administration of felodipine once daily was confirmed by the results of the follow-up study during which 81% of the patients remained completely free of symptoms and signs of myocardial ischemia.

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Effects of Daily High-Intensity Exercise on Myocardial Perfusion in Angina Pectoris

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Forty male patients with chronic stable angina pectoris and no prior myocardial infarction were studied by planar thallium scintigraphy with use of circumferential profile analysis. Ischemic defects were assessed by measuring degrees of circumference involved and area of defect. Data were collected for 3 vascular regions in each of 3 views (anterior, 45° and 65° left anterior oblique projection). Patients were then randomized to exercise and control groups, the former training for a period of 1 year using the Canadian Airforce plan for physical fitness. After 1 year, both groups were restudied. Exercise training produced a 34% reduction in degrees of ischemia overall ($p < 0.02$), the most significant change being seen on the anterior view (72° ± 59° before vs 30° ± 35° after training). Regional analysis showed markedly improved perfusion anterolaterally and apically on the anterior view and anteroseptally on the 65° left anterior oblique view. These improvements support the hypothesis that exercise training improves myocardial perfusion by enhanced collateral function.

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In his animal studies, Eckstein[1] demonstrated that significant coronary artery narrowing in dogs stimulated the development of an effective collateral circulation and that this collateralization could be further developed by exercise to produce large collateral vessels capable of protecting against myocardial infarction. Some 30 years on we lack conclusive evidence that the same can be achieved in humans. Exercise training has been advocated for the rehabilitation of patients after myocardial infarction,[2–6] cardiac surgery[7–11] and angina pectoris.[12–16] Such a recommendation has its foundation in peripheral adaptations to exercise training which result in a reduced myocardial work load, rather than in convincing evidence of genuine myocardial benefit. Recent studies suggest that prolonged high-intensity exercise may have some effect.[15–18] This study was undertaken to examine whether exercise training of high intensity in the presence of stress-induced myocardial ischemia could produce improvements in myocardial perfusion and, if so, whether such improvements would be in keeping with the findings in Eckstein's animal model.

METHODS

Patients: Forty men <60 years of age were recruited. Chronic stable angina ≥6 months' duration and a positive exercise tolerance test were essential for inclusion. Exclusion criteria included previous myocardial infarction, coronary bypass surgery or angioplasty, recent unstable angina, diabetes mellitus, uncontrolled hypertension, valvular heart disease and physical handicap. Beta-blocker therapy was withdrawn for 4 weeks. Any patient who could not be maintained without β blockers was withdrawn from the study. A diagnostic exercise tolerance test was performed. A test was deemed positive when 1 mm of horizontal or downsloping ST depression was recorded 80 ms after the J point in a lead with no ST depression at rest or a further 1 mm of ST depression in a lead showing change at rest. After exercise testing, nifedipine was prescribed for symptomatic control when necessary, with nitrates for patients who could not tolerate nifedipine or who required additional antianginal therapy. Sublingual glyceryl trinitrate was also allowable. Subsequent use of β-blocker therapy during the study period necessitated withdrawal from the study.

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Thallium-201 scintigraphy: Thallium-201 scintigraphy was performed 1 week after diagnostic exercise tolerance testing. After an overnight fast and no medication for 24 hours, a symptom-limited treadmill exercise tolerance test was performed. An intravenous cannula was inserted into the left antecubital vein before exercise. Stress testing was performed using a modified Naughton protocol consisting of a constant 3 miles/hour with an initial gradient of 0%.[19] The gradient was increased by 2.5% at 3-minute intervals providing an incremental increase in work load of approximately 1 metabolic equivalent (MET) per stage of exercise, thus ensuring a reproducible end point. Eighty megabecquerels of thallous-201 chloride was injected through the cannula and flushed with 20 ml of 0.9% sodium chloride 1 minute before the end of exercise. After exercise the patient was scanned using a gamma camera with a large field-of-view crystal and general-purpose low-energy parallel-hole collimator. Images were obtained in the anterior, and 45° and 65° left anterior oblique projections, data being stored in a 128 × 128 × 8-bit matrix on computer. The system was set to acquire a fixed number of counts for each view (350,000) and the time taken to do so was recorded. The spleen was masked. Redistribution images were recorded 3 hours after initial stress images to confirm reversibility of ischemic defects. Imaging time for the redistribution images was the same as the time taken to acquire the stress images. Stress images were obtained within 30 minutes of cessation of exercise.

The images thus obtained were further processed according to accepted quantitative methods. A background subtraction program was applied to the images to correct for noncardiac background.[20,21] Thereafter, the operator identified the center and apex of the left ventricle on each view. The program then generated 60 radii at 6° intervals from the center of the ventricle, commencing with the first radius (0°) at 90° counterclockwise from the marked apex and subsequent radii at 6° intervals clockwise from the 0° radius. Each radius was then searched for the hottest pixel. These were highlighted on the screen and if accepted by the operator, each pixel was averaged with the 2 adjacent pixels on that radius. The hottest count thus obtained was assigned a value of 100% and all other radii assigned a value in proportion to this. The values for the redistribution image were also expressed as a percentage of maximum stress value. On the stress profile, ischemia is identified as an area with relatively low initial uptake of thallium with a tendency to normalize on the 3-hour view.

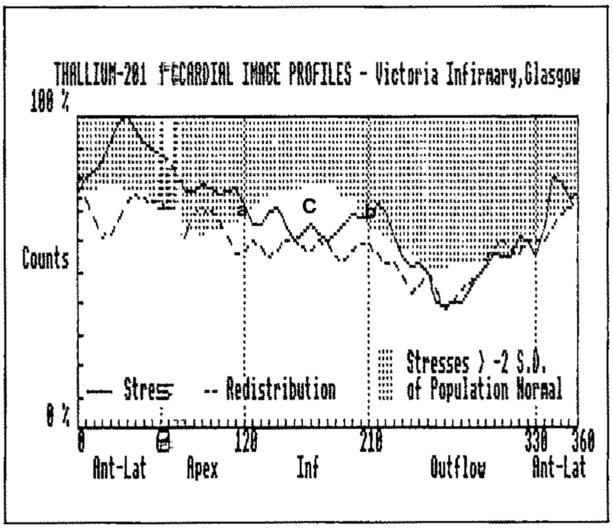

FIGURE 1. Calculation of ischemic degrees and area from circumferential profile. a–b = ischemic degrees; C = ischemic area calculated by subtracting area under patient's curve between a and b from area under normal curve between a and b.

To obtain a benchmark of normality with which to compare defects these images were further processed. First, a 3-point circumferential smoothing was performed using a program developed in our department. The profiles thus obtained were superimposed on a range of normal values. Because these values are only a benchmark of normality and not absolute zeros, it was believed unnecessary and unethical to acquire our own group of normal persons. The values used therefore were obtained from published data produced by Maddahi[22] and Abdulla[23] and their co-workers. These values identify lower limits of normality equivalent to 2 standard deviations below the mean for a group of subjects with low risk of coronary disease. By superimposing the patient's profile on this normal range, an area of abnormality could be identified where the patient's scan fell below this range. The number of degrees of circumference that were abnormal could be calculated as could the area of abnormality (the area between the patient's and the normal curve in the ischemic zone) (Figure 1).

At the end of the study repeat scanning was performed by exercising the patient to his new symptom-limited maximum heart rate. Because this introduces a variable (heart rate) that might affect the area of abnormality, a third parameter was calculated by dividing the area of abnormality by maximum heart rate achieved (the SIS score). A similar technique has been used by other investigators and found to correlate well with the extent of angiographic disease.[24]

We have found the aforementioned technique to accurately demonstrate the most ischemic areas in middle-aged male patients where breast attenuation and other artefacts are less common. We took the further precaution of comparing the abnormalities documented by this technique with a subjective visual assessment of the scans. There was no significant discrepancy between the computer-derived abnormality and the subjective zone of ischemia.

Training program: After thallium scintigraphy, patients were randomly allocated to training and control groups. The training group undertook the Canadian Airforce Program for Physical Fitness.[25] This is a brief 11-minute daily exercise program of 5 callisthenic exercises requiring no equipment. It was prescribed for daily home use, with exercise levels increasing in intensity at weekly intervals to achieve a progressive increase in physical fitness. Patients moved to the next level if the previous level could be completed within 11 minutes without excessive chest pain or dyspnoea. No limit was placed on the maximum exercise level. A weekly hospital supervised session was used to initiate new patients and monitor early progress. During the first session patients were monitored for arrhythmias. After introduction to the program subsequent attendance at the supervised session was optional.

The control subjects were informed that mild exercise may be beneficial and were advised with respect to diet and smoking habits. They were formally followed up at 3-month intervals throughout the study, as was the exercise group, but were granted open access to the controlling physician at any time in order to counteract possible bias resulting from weekly contact with the exercise group.

Statistical analysis: For the 3 parameters calculated, global data were obtained by summating the results from all 3 views. These data were found to conform to a normal distribution. Intragroup comparison of means and interval change data were obtained using a Student's *t* test for unpaired and paired data, respectively. Data for views and regions were not normally distributed and were therefore analyzed using a Wilcoxon signed rank test for paired data. All results are expressed as mean ± standard deviation with p values and 95% confidence intervals.

RESULTS

Demographic data relating to the exercise and control groups are listed in Tables I and II. There were no significant differences between the groups. During the study, 2 patients in the exercise group and 1 control patient succeeded in stopping smoking. There was a trend toward reduction in weight in the exercise group over the study period.

The simple format of the exercise program proved to be "user friendly" and compliance was high. During the period of study, 1 patient in the exercise group defaulted and 1 was withdrawn because he developed unstable angina requiring β blockade. Another patient could not be restudied. Two control subjects were lost to follow-up and 1 died. The baseline scan results of another patient were inadvertently destroyed. Of the original 40 patients, 17 in the exercise group and 16 control subjects were successfully studied on 2 occasions. In addition, 1 patient from each group sustained a full-thickness myocardial infarction during the study, radically altering the shape of the circumferential profiles and making comparison of pre- and poststudy scans impossible. Results given therefore apply to 16 patients who exercised and 15 control subjects.

TABLE I Demographic Data: Exercise Group

Pt. No.	Age (yr)	Duration of Angina (mos)	Cigarette Smoker	Height (inches)	Weight (lbs)
1	51	24	Ex	74	220
2	55	8	Ex	70	175
3	47	10	0	69	190
4	45	24	Ex pipe smoker	70	188
5	57	6	Ex	68	165
6	55	12	Ex	64	142
7	60	36	Ex	68	136
8	51	6	Ex	72	221
9	52	9	+	64	159
10	55	60	+	74	198
11	52	8	+	74	215
12	60	24	0	70	188
13	48	6	Ex	68	148
14	59	18	0	67	140
15	57	108	0	67	150
16	58	6	0	68	196
17	48	12	+	68	198
18	46	12	Ex	69	204
19	48	6	0	67	182
20	58	6	Ex	72	220
Mean	53	20	NA	69	182
± SD	—	25	NA	3	28

NA = not applicable; SD = standard deviation.

TABLE II Demographic Data: Control Group

Pt. No.	Age (yr)	Duration of Angina (mos)	Cigarette Smoker	Height (inches)	Weight (lbs)
21	57	8	0	62	127
22	60	96	0	73	191
23	54	10	Ex	69	187
24	50	12	+	70	175
25	55	6	0	67	166
26	48	15	0	68	181
27	53	10	Ex	71	190
28	53	6	Ex	73	225
29	56	6	0	68	170
30	48	6	Ex	71	184
31	40	8	Ex	70	214
32	53	12	+	70	205
33	49	6	+	66	159
34	60	9	0	68	170
35	37	6	+	66	181
36	56	6	Ex	68	165
37	50	12	+	66	143
38	46	6	Ex	68	171
39	45	8	0	70	216
40	50	6	Ex	68	190
Mean	51	13	NA	69	181
± SD	—	10	NA	3	24

Abbreviations as in Table I.

The exercise tolerance data for this group of patients have previously been published.[26] A training ef-

TABLE III Global Thallium Data

Pt. No.	Degree Before	Degree After	Area Before	Area After	SIS Score Before	SIS Score After
			Exercise Group			
1	234	156	1,352	1,212	19	17
2	120	150	793	1.296	10	17
3	210	234	2,666	3,214	37	44
4	42	96	202	919	3	10
5	[illegible]	48	1,979	139	20	1
6	402	156	8,345	745	98	9
7	264	108	1,879	1,013	35	16
8	276	228	2,372	2,111	37	27
9	78	0	554	0	8	0
10	150	12	1,930	10	26	0
11	30	108	187	512	2	6
12	204	72	1,602	480	27	6
13	318	270	4,451	4,590	60	61
14	54	36	298	114	3	1
15	276	216	2,952	2,512	36	26
16	312	156	3,727	2,313	48	30
Mean	[illegible]	128	2,206	1,330	29	17
± SD	[illegible]	82	2,060	1,327	25	17
95% CI	20–114		—		0–25	
p Value	<0.02		NS		<0.05	
			Control Group			
21	276	138	2,259	1,552	35	25
22	300	264	5,067	3,267	85	52
23	192	108	1,902	1,022	24	14
24	36	102	245	470	4	7
25	360	318	6,837	3,656	91	55
26	144	192	984	1,461	11	16
27	174	156	1,438	1,140	20	16
28	78	96	859	1,850	10	20
29	18	84	35	285	1	4
30	30	114	111	718	1	7
31	210	90	2,755	295	33	4
32	330	384	7,821	9,056	122	137
33	12	96	55	334	1	4
34	[illegible]	180	1,710	1,500	18	17
35	[illegible]	48	1,011	277	12	3
Mean	[illegible]	158	2,206	1,792	31	25
± SD	121	96	2,460	2,260	38	35
95% CI	—		—		—	
p Value	NS		NS		NS	

CI = confidence interval; NS = not significant; SD = standard deviation.

TABLE IV "View" Thallium Data in the Exercise Group

Patient No.	Anterior Before	Anterior After	45° Before	45° After	65° Before	65° After
1	78	72	42	0	114	84
2	0	0	48	72	72	78
3	84	102	114	120	12	12
4	30	0	0	84	12	12
5	6	0	96	42	0	6
6	192	42	78	30	132	84
7	96	96	102	12	96	0
8	120	0	102	102	24	126
9	30	0	42	0	6	0
10	150	0	0	12	30	0
11	0	0	48	60	12	48
12	132	12	42	42	30	18
13	0	0	186	192	132	78
14	54	12	0	24	0	0
15	102	84	120	132	54	0
16	72	66	36	0	204	90
Mean	72	30	66	58	58	40
± SD	59	35	51	56	61	43
p Value	<0.05		NS		NS	

Abbreviations as in Tables I and III.

fect was achieved as measured by a reduction in heart rate at rest of 5 beats/min and in a submaximal heart rate of 13 beats/min. Maximum heart rate was increased by 10 beats/min in the training group. These changes were all statistically significant (p <0.05). Maximum ST depression was reduced from 1.9 ± 0.9 to 1.6 ± 1.2 mm (p <0.05) despite the increase in maximum heart rate. Time to 1 mm ST depression was increased by 135% (374 ± 749 to 881 ± 668 seconds). Treadmill time improved from 741 ± 356 to 1,272 ± 514 seconds after training (72% increase, p <0.001). As a result, maximum treadmill work load increased from 5.6 ± 1.3 to 9.7 ± 2.8 METS. Over the same period there were no significant changes in the control group.

The exercise group noted marked symptomatic improvement within 8 weeks of commencing training. At 1 year, 6 patients had become asymptomatic; they and 2 other patients discontinued antianginal therapy with nifedipine. The only patient who increased drug therapy in the exercise group during the study was the patient who developed unstable angina. Three control subjects increased their dosage of nifedipine, and 1 patient, subsequently found to have sustained a myocardial infarct, required the addition of nitrates.

Heart rate monitoring during exercise confirmed that the exercises were of high intensity; mean maximum heart rate noted during ambulatory monitoring was in excess of the maximum treadmill heart rate.

Table III lists the results of the 3 parameters of global perfusion. The exercise group had a 34% reduction in mean extent of ischemia as measured by degrees of circumference involved. The ischemic area was reduced similarly by 40% after training, but because of much wider standard deviations for these measurements, this difference just failed to reach statistical significance. When this area is corrected for heart rate, however, the reduction in SIS score from 29.3 to 16.9 is significant at the 5% level.

The results for the control group were not significant for any of the 3 parameters. Indeed, the degrees of abnormality differed by 5° only over the year; such a difference represented <1 point on a circumferential profile. Small reductions in mean area of abnormality and SIS score may simply reflect a greater variability in depth of abnormality compared with degrees of abnormality. Intergroup comparison of interval change data shows the reduction in ischemia of 67° after exer-

TABLE V Regional Thallium Data from the Exercise Group

	Anterior						45° Left Anterior Oblique						65° Left Anterior Oblique					
	Anterolateral		Apical		Inferior		Posterolateral		Inferoapical		Septal		Inferior		Apical		Anteroseptal	
Pt. No.	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	0	0	24	0	54	72	18	0	18	0	6	0	66	60	18	24	30	0
2	0	0	0	0	0	0	48	66	0	6	0	0	72	78	0	0	0	0
3	0	12	0	30	84	72	12	12	12	36	90	72	12	54	0	0	0	0
4	12	0	18	0	0	0	0	0	0	0	0	84	0	0	0	0	12	12
5	6	0	0	0	0	0	0	0	6	0	90	42	0	6	0	0	0	0
6	90	0	60	0	42	42	0	0	0	0	78	30	0	0	42	0	90	84
7	0	0	24	30	72	66	0	0	42	6	60	6	66	0	64	0	24	0
8	60	24	42	12	18	0	78	66	24	36	0	0	24	78	0	48	0	0
9	0	0	12	0	18	0	0	0	0	0	42	0	0	0	0	0	6	0
10	30	0	30	0	90	0	0	0	0	0	0	12	30	0	0	0	0	0
11	0	0	0	0	0	0	30	36	18	24	0	0	12	48	0	0	0	0
12	24	12	60	0	48	0	0	0	0	0	42	42	18	18	12	0	0	0
13	0	0	0	0	0	0	54	42	60	60	72	90	60	48	60	30	12	0
14	0	0	0	0	54	12	0	24	0	0	0	0	0	0	0	0	0	0
15	36	0	66	0	0	84	0	0	18	42	102	90	0	0	24	0	24	0
16	0	0	0	0	72	66	24	0	12	0	0	0	78	78	54	12	72	0
Mean	16	3	21	4	35	26	17	15	13	13	36	29	27	29	17	7	17	6
±SD	26	7	24	10	34	34	24	24	17	20	39	36	30	33	24	14	27	21
p Value	<0.05		<0.02		NS		NS		NS		NS		NS		NS		<0.05	

Abbreviations as in Tables I and III.

cise training to be significantly better than the reduction of 5° in control subjects ($p < 0.05$).

Because of these positive global results, the ischemic degree data for the exercise group were further broken down to show whether the improvements demonstrated could be ascribed to any of 3 views used (Table IV) or to any of the 9 vascular regions (Table V). The anterior view showed a significant improvement. Although neither the 45° or 65° views showed statistically significant change, both had small reductions in ischemic degrees.

The regional data show which vascular regions produced improvement. The anterolateral and apical regions on the anterior view both showed significant improvements in number of ischemic degrees. On the 65° view the anteroseptal region improved in a similar fashion. Although no other regions showed statistically significant improvements, the apical region on the 65° view showed a similar large reduction. The figures for the inferior region on the anterior view and the septal region in the 45° view showed smaller improvements, and the 3 remaining regions showed little change.

DISCUSSION

A number of studies have addressed the question of myocardial perfusion and exercise training using thallium scintigraphy.[27-31] Verani et al[27] studied 16 patients on a 12-week training program using thallium-201 scintigraphy. There are limitations in his study in terms of duration of training program and lack of control subjects. In addition, the thallium scintigraphy technique is open to criticism. They chose to have their patients exercise to the same level of cardiac work before and after training. This theoretically allows one to compare perfusion at comparable work loads. If, however, maximal cardiac work is improved by training, the second scan is performed below the ischemic threshold, a situation not generally recommended for assessment of thallium scans. Verani found that conditions in 3 patients improved, in 3 they deteriorated, and in 10 they remained unchanged; they concluded that there was no improvement in myocardial perfusion.

Tubau et al[28] used circumferential profile analysis, but profiles were used only to establish the presence of defects, and observers compared paired scans to visually assess improvement or deterioration. This insensitive technique meant that although 132 abnormal regions were detected initially, only 13 of these were judged to have changed.

One of the largest studies of exercise training was reported by Froelicher et al[29] in 1984. A randomized controlled study of 146 patients over a 1-year period was performed using a thallium technique similar to that of Verani but with a more extensive semiquantitative scale. Analysis of variance demonstrated that improved perfusion after exercise training depended on the presence of angina. It was concluded that any improvement was small and of limited clinical significance. In 1986, the results of a subgroup of this study by Sebrechts et al[30] were subjected to further analysis by circumferential profiles measuring ischemic areas. The parent study by Froelicher had already shown improvements in perfusion and made the significant point that angina was an important prerequisite for that improvement. This study applied a figure to those results but did not reveal new information. The results of regional analysis confused the picture, revealing 3 regions of improvement in 3 different vascular territories on 3 different views. Improvement in the left anterior descending territory on the anterior view, e.g., is not reinforced by improvements in other left anterior descending regions. This suggests that the results may be spurious, and because of the nonmaximal scanning used on the second occasion, one must ask whether alterations in perfusion in the exercise group are simply a reflection of technique.

The best study to date was published by Schuler et al.[31] He studied 18 patients with stable angina pectoris and hyperlipidemia and observed changes with a combination of low fat diet and exercise training over 1 year. Thallium scanning was performed at maximal exercise on both occasions, and the degrees of circumference of the left ventricle with reversible ischemia were measured from reconstructed cross-sectional images of stress and redistribution scans. Stress-induced myocardial ischemia measured in this way was reduced by 54% ($p < 0.05$) despite the higher work load. The study was limited by lack of regional data and by the dual pathology of 1 group and the dual nature of the intervention; nonetheless, it is the one study in which the changes demonstrated cannot readily be explained other than by improvements in myocardial perfusion.

This study provides convincing evidence of improved myocardial perfusion after exercise training. The reduction in number of degrees of ischemia by 34% despite an increase in cardiac work is comparable to Schuler's results. In this study, however, the reduction in ischemic degrees is significant both by intra- and intergroup analysis, strengthening the case that it is due to the intervention and not to natural change as a result of the disease. Whereas the area data show a larger percent change, they do not add to the degree results; the major change appears to be a reduction in the size of the ischemic zone as measured by degrees of circumference involved rather than in the depth of ischemia within that zone as measured by area of ischemic curve. The simplest explanation is that the maximum depth of the ischemic zone may correlate with symptom-limited exercise tolerance, and because the scans were performed to symptom limitation rather than matched for work load, one would inevitably expect to produce similar depth of ischemia. Alternatively, collateralization may have occurred by intervessel anastomoses in the periphery of the ischemic zone rather than by intravessel collaterals that would improve anterograde flow to the center of the ischemic zone.

Analysis of the 3 views shows the only significant improvement to be in the anterior view. Redistribution of thallium occurring after cessation of exercise may mask ischemic change on later views. The 9 regional views provide evidence for genuine regional improvement in ischemia and support the hypothesis of collateralization. Regions with improved perfusion fit into the territory of the left anterior descending coronary artery with significant changes anterolaterally on the anterior view and also anteroseptally on the 65° left anterior oblique view. Furthermore, the apical improvements are significant in the anterior view and, although not significant in the 65° view, are substantial here also. That these apical changes may also be subscribed to the left anterior descending artery is supported by the lack of change inferolaterally, posterolaterally and inferiorly. One can conclude from these studies that exercise training has induced changes in myocardial perfusion in the anterior wall of the left ventricle in the territory of the left anterior descending coronary artery. The localized nature of these changes supports the hypothesis that collateralization is the mechanism of improvement rather than some general cardiac effect which might be expected to have a more global effect on perfusion. The consistency of these results in all 3 views adds to the conviction that these changes are genuine and not spurious.

That these changes have occurred in the left anterior descending territory may be coincidental. However, thallium studies show that disease in this artery produces larger defects, making changes more readily detected.[32,33] Iskandrian[34] and Tubau[35] and their coworkers showed that defects were smaller in the presence of collaterals, but Iskandrian found this to be significant only for the left anterior descending artery. Postmortem angiography has shown the left anterior descending artery to be the most frequently involved in both inter- and intravessel collateral formation.[36] This may be partly due to its complex branching or to the fact that disease of this vessel, unlike the right coronary or circumflex arteries, is most often found in its midportion, allowing many potential sources for collateralization.[37] Furthermore, collaterals are more common in patients with 1-vessel disease and this most often occurs in the left anterior descending artery.[37] All of these facts may explain why improvement shown in this study is in the left anterior descending territory.

The group in this study was carefully selected. Angina pectoris was a prerequisite for entry, and all patients therefore conformed to the group found by Froelicher to gain most benefit. In addition, exclusion of patients with infarcts not only increased the likelihood of improvement, but also simplified the investigative technique since all abnormalities detected on stress scanning were potentially reversible. These factors, in addition to a careful choice of exercise duration and high-intensity exercise, are the most likely reasons why this study has succeeded in demonstrating improved perfusion.

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Silent Versus Symptomatic Ischemia During a Thallium-201 Exercise Test

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One hundred thirty-four patients with redistribution on a thallium-201 exercise test who did not experience angina (group 1) were compared with 134 patients also having redistribution who had angina during the test (group 2). The groups were matched by age, sex, and peak exercise heart rate. Although patients in both groups achieved an equivalent exercise level, patients in group 1 had less frequent (53 vs 71%, p <0.005) and less severe (0.15 ± 0.13 vs 0.20 ± 0.13 mV, p <0.005) ischemic ST-segment depression. Group 1 also had less ischemic thallium-201 images in terms of the number of redistributing defects, the severity of the worst redistributing defect, and an ischemic index composite of both extent and severity. Patients in group 1 were less likely to undergo early revascularization (12 vs 29%, p <0.005), but in the remaining patients the occurrence of adverse cardiac events was similar (21% vs 29%, p = not significant). By multivariate analysis, only the ischemic index correlated with early revascularization in group 1 (p = 0.0017), whereas the percent maximal predicted heart rate correlated best in group 2 (p = 0.0003). In group 1 the ratio of lung/heart thallium-201 uptake correlated best with an outcome of nonfatal myocardial infarction or cardiac death (p = 0.0024); in group 2 the presence of fixed left ventricular dilatation did (p = 0.0022). Thus, patients with exercise-induced thallium-201 redistribution without angina have less ischemia than patients experiencing angina. They are also less likely to undergo early revascularization, but their prognosis is otherwise similar to patients with angina during the test.

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Despite many previous studies, the differences between silent and symptomatic myocardial ischemia during an exercise stress test remain unclear. Whereas some studies have suggested that patients without angina have less myocardial ischemia than patients with angina,[1,2] others have shown no difference.[3–7] Studies that have compared differences in prognosis are equally variable, with there being evidence of no difference,[1,5,8–10] evidence of a worse prognosis,[3,11] and evidence of a better prognosis[2,12] for patients with silent ischemia. Another factor adding to the uncertainty is that different criteria have been used to define exercise-induced silent ischemia. Most investigators have used the development of ischemic electrocardiographic changes,[2,8–10,13] whereas others have used evidence of ischemia from radionuclide studies.[1,3,4,6–8] Most studies have had a selection bias in that only patients with coronary artery disease documented by cardiac catheterization were included, which may not have accurately represented the entire population of patients with exercise-induced silent ischemia studied noninvasively. Finally, in many of these studies the exercise levels achieved by the compared groups were not the same.[2–5,7,8,10]

In this study we sought to overcome these limitations. Our study population was derived from consecutive outpatients who had ischemia during a thallium-201 exercise test, regardless of whether they underwent coronary angiography. Ischemia was defined as the occurrence of a redistributing perfusion defect. Furthermore, patients without angina during the test were matched to patients with angina by age, sex, and peak heart rate. The extent and severity of ischemia, and the clinical outcomes over 5 years were compared in both groups.

METHODS

Patients: From the approximately 4,900 patients presenting to our institution for an outpatient thallium-201 exercise test from September 1982 to December 1988, all having at least 1 unequivocal redistributing defect were identified. Patients with a previous revascularization procedure were excluded. Patients not experiencing angina during the test were selected (group 1) and blindly matched by sex, age (within 2 years), and peak exercise heart rate (within 6 beats/min) to pa-

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tients experiencing angina during the test (group 2). Every patient who could be matched was included, yielding 134 matched pairs, a total of 268 patients.

Exercise protocol and image acquisition: Each patient underwent a symptom-limited treadmill exercise test using a Bruce or modified Bruce protocol, with continuous monitoring of heart rate and rhythm, blood pressure and symptoms. Twelve-lead electrocardiograms were recorded every minute. At peak exercise, 2 to 3 mCi of thallium-201 chloride was injected intravenously. Stress and 4-hour delayed myocardial planar images were obtained in the 3 standard projections.[14]

Analysis of stress tests: For each patient the stress electrocardiograms and accompanying information were reviewed without knowledge of other data. The peak heart rate, age-adjusted maximal predicted heart rate, work load in metabolic equivalents,[15] peak rate pressure product and exercise time were noted, as was the presence and magnitude of ST-segment depression. An electrocardiographic response was defined as positive for ischemia if there was horizontal or downsloping ST-segment depression $\geq$0.1 mV for $\geq$80 ms after the J point for $\geq$3 consecutive beats. The electrocardiograms of patients with left bundle branch block, ST-segment abnormalities at rest, or of those taking digitalis were considered inconclusive. A systolic blood pressure increase of $\geq$10 mm was defined as normal. Finally, the presence of exercise-induced ventricular ectopy was noted.

The presence of anginal discomfort during the test was ascertained from the reports of experienced cardiologists who performed and interpreted the tests. To be included in the group with chest pain, the discomfort had to be suggestive of angina or similar to the patient's presenting symptoms. Patients who only had dyspnea during the test were not included in the chest pain group, although it is conceivable that dyspnea in some cases may have been an anginal equivalent.

Analysis of thallium-201 images: All images were reviewed by 3 of the authors unaware of other data. Only patients with unequivocal redistributing defects seen in multiple views and confirmed by quantitation[16] were included. All images were reviewed from November to December of 1989, eliminating possible variation of image interpretation related to the time of the test.

The left ventricle was divided into 3 segments in each projection (Figure 1). Each segment was visually graded on a 5-point scale: (4 = normal, 3 = mildly reduced uptake, 2 = moderately reduced uptake, 1 = severely reduced uptake, 0 = minimal to no uptake). An increase of 1 grade from stress to delayed image was interpreted as redistribution. The number of fixed defects, the number of redistributing defects, and the grade (in the stress image) of the worst redistributing segment was noted. A qualitative ischemic index, encompassing both the extent and severity of ischemia, was derived (Figure 1).[17,18]

The segments were also graded quantitatively using a previously described computer algorithm.[16] The presence or absence of initial defects and redistribution were derived from data obtained from normal subjects with a <1% probability of coronary artery disease. A quantitative ischemic index was derived in a manner analogous to the qualitative index.

Images were also reviewed for the presence of cavity dilatation, both fixed and transient, and lung uptake.[19,20]

Follow-up analysis: Follow-up was obtained for 98% of patients to a mean of 25 ± 19 months after the test (p = not significant between the groups) from hospital and outpatient records, personal communications with the private physician, data from the Bureau of Vital Statistics, or telephone interviews. Cardiac events considered were: cardiac death, nonfatal myocardial infarction, a revascularization procedure (coronary artery bypass surgery or percutaneous transluminal coronary angioplasty) performed >6 months after the exercise test, and a revascularization procedure performed at any time that was precipitated by clinical deterioration. The first event was the end point. Patients who died of noncardiac causes were treated as event-free until their death and then censored. Because a revascularization procedure is frequently based on test results rather than clinical deterioration, elective early (within 6 months) procedures were considered separately.

Statistical analysis: All values are expressed as mean ± 1 standard deviation. Continuous variables were compared by an unpaired 2-sample *t* test. Proportions were compared by the chi-square statistic with the Yates correction. Event-free survival was calculated by

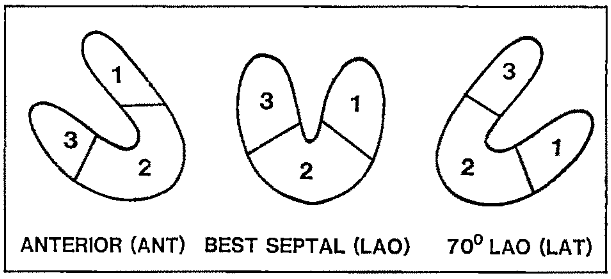

FIGURE 1. The left ventricle was divided as shown. Thallium-201 uptake was graded visually using a 5-point scale. Each redistributing segment was given an ischemic score of 1 − stress grade/4 (i.e., the percent decrease from normal in thallium uptake); normal and fixed segments were given scores of 0. The 9 segments were grouped into 6 anatomic regions: anterior, lateral (ANT 1, LAT 3), inferior (ANT 3, LAT 1), apex (ANT 2, LAT 2), septum (left anterior oblique [LAO] 3), inferoapex (LAO 2), posterolateral (LAO 1). For the anterior, inferior and apical walls, the scores of the 2 corresponding segments were averaged. These values were added to the remaining 3 wall scores to derive the ischemic index. The ischemic index could range from 0 (best) to 6 (worst).

TABLE I Baseline Clinical and Angiographic Characteristics

Variable	Group 1* (n = 134)	Group 2† (n = 134)	p Value
Clinical			
Age (years)	62 ± 8	62 ± 8	NS
Men	129 (96)	129 (96)	NS
Prior angina	78 (58)	121 (94)	<0.001
Prior infarction	46 (34)	38 (28)	NS
Risk Factors			
Diabetes mellitus	15 (11)	14 (10)	NS
Smoking	73 (54)	58 (43)	NS
Hypertension	74 (56)	69 (51)	NS
Medications			
Nitrates	54 (40)	49 (37)	NS
β blockers	68 (51)	79 (59)	NS
Diltiazem/verapamil	38 (28)	38 (28)	NS
Angiographic Data			
Angiography performed	79 (59)	93 (69)	NS
Vessels diseased	2.2 ± 0.9	2.3 ± 0.9	NS
Multivessel disease	62 (79)	71 (77)	NS

*Group 1 = patients with silent treadmill ischemia.
†Group 2 = patients with symptomatic treadmill ischemia.
Numbers in parentheses refer to percentages of patient group.
NS = not significant.

TABLE II Exercise Test Results

Variable	Group 1 (n = 134)	Group 2 (n = 134)	p Value
Work Load			
Peak HR (beats/min)	131 ± 21	132 ± 21	NS
MPHR (%)	79 ± 12	79 ± 12	NS
METs	9.3 ± 3.1	8.9 ± 3.0	NS
Peak RPP/1,000	23.1 ± 6.3	22.4 ± 5.7	NS
Exercise time (min)	8.0 ± 2.6	7.4 ± 2.8	NS
Electrocardiographic Results			
Positive	71 (53)	95 (71)	<0.005
Negative	37 (27)	20 (15)	<0.05
Inconclusive	26 (20)	19 (14)	NS
Maximal ST Dep (mV)	0.15 ± 0.13	0.20 ± 0.13	<0.005
Blood Pressure Response			
Normal	113 (84)	96 (72)	<0.05
Ventricular Ectopy			
Present	60 (45)	55 (41)	NS

Numbers in parentheses refer to percentages of patient group.
ECG = electrocardiogram; HR = heart rate; Maximal ST Dep = maximal ST depression developed during the exercise test; METs = estimated metabolic equivalent level at maximal exercise; MPHR (%) = percent of maximal predicted heart rate for age achieved; NS = not significant; RPP = rate pressure product (heart rate × systolic blood pressure at peak exercise).

life-table analysis. To assess the prognostic power of the different exercise and thallium variables, stepwise logistic regression and Cox proportional-hazards survival analysis was performed (BMDP LR and BMDP 2L: Department of Biomathematics, University of California at Los Angeles). The following variables were analyzed: age, use of *β* blockers, exercise time, metabolic equivalents, percent maximal predicted heart rate achieved, peak heart rate, rate pressure product, blood pressure response to exercise, presence of electrocardiographic evidence of ischemia, number of redistributing defects, severity of the worst redistributing defect, ischemic index, presence of increased lung uptake, lung/heart activity ratio, transient left ventricular dilatation, fixed left ventricular dilatation, and dilatation either transient or fixed. For all statistical analyses, differences were considered significant for a p value <0.05.

RESULTS

Patient characteristics: The baseline characteristics of the patients in each group are compared in Table I. Fewer of the patients in group 1 (silent ischemia during exercise) had a previous history of chest pain. There was no difference between the groups in cardiac risk factors, including diabetes mellitus, nor in the percentages of patients receiving various cardiac medications. The proportion of patients in each group undergoing cardiac catheterization was similar, as was the extent of coronary disease. Four of the patients in group 1 (5%) and 2 in group 2 (2%) who underwent cardiac catheterization had no apparent epicardial disease.

Comparison of ischemia: Despite virtually identical work loads attained by both groups, patients in group 1 had a less ischemic electrocardiographic response to exercise (Table II). Patients in group 1 had less frequent and less severe ischemic ST-segment depression. They were also more likely to have had a normal blood pressure response to exercise. The incidence of ventricular arrhythmias was similar in both groups.

Patients in group 1 had less ischemic thallium-201 images (Table III). By visual analysis, there were fewer redistributing defects per patient. The mean stress grade of the worst redistributing defect for patients in group 1 was higher, and both the visual and quantitative ischemic indexes were lower in group 1. There was no difference between the groups in the proportion of patients with abnormal lung uptake, the severity of lung uptake, or the presence of either transient or fixed left ventricular dilatation. When analysis was limited to the subgroup of patients with ischemic electrocardiograms or to those with proven coronary disease, patients in group 1 still had less extensive and less severe redistributing defects than patients in group 2.

Follow-up: Fewer patients in group 1 (12 vs 29%, p <0.005) underwent an early (within 6 months) elective revascularization procedure (Table IV). However, there was no significant difference in late revascularization, revascularization after clinical deterioration, nonfatal myocardial infarction or cardiac death in the remaining patients. The overall incidence of an event was similar: 21% in group 1, 29% in group 2. The outcomes of the 2 groups by life-table analysis, excluding patients with early revascularization, are seen in Figures 2 and 3.

TABLE III Comparison of Thallium-201 Scintigraphic Variables

Variable	Group 1 (n = 134)	Group 2 (n = 134)	p Value
Visual Analysis			
No. of fixed defects/pt.	0.7 ± 1.1	0.5 ± 0.9	NS
No. of redistributing defects/pt.	3.3 ± 1.4	3.8 ± 1.4	<0.005
Stress grade of worst redistributing defect*	1.6 ± 1.1	1.3 ± 0.9	<0.05
Ischemic index	1.1 ± 0.7	1.3 ± 0.7	<0.005
Quantitative Analysis			
No. of fixed defects/pt.	1.9 ± 1.5	1.7 ± 1.7	NS
No. of redistributing defects/pt.	3.2 ± 2.0	3.6 ± 2.0	<0.10
Stress grade of worst redistributing defect†	59 ± 15	56 ± 14	<0.10
Ischemic index	0.38 ± 0.52	0.52 ± 0.55	<0.05
Lung			
Increased lung uptake	80 (60)	78 (58)	NS
Lung/heart ratio	0.4 ± 0.1	0.4 ± 0.1	NS
LV Dilatation			
Absent	61 (46)	48 (36)	NS
Transient	55 (41)	73 (54)	NS
Fixed	18 (14)	13 (10)	NS

*Range = 0–4; †Range = 0–100.
Numbers in parentheses refer to percentages of patient group.
LV = left ventricular; NS = not significant.

TABLE IV Cardiac Events During Follow-Up

	Group 1 (n = 130)*	Group 2 (n = 132)†	p Value
Early Revascularization			
CABG	13 (10)	35 (27)	<0.001
PTCA	3 (2)	3 (2)	NS
Total	16 (12)	38 (29)	<0.005
Remaining Patients			
	(n = 114)	(n = 94)	
Late revascularization	5 (4)	9 (10)	NS
Revascularization after deterioration	5 (4)	8 (9)	NS
Nonfatal MI	6 (5)	6 (6)	NS
Cardiac death	8 (7)	4 (4)	NS
Total events	24 (21)	27 (29)	NS

*Four patients lost to follow-up.
†Two patients lost to follow-up.
Numbers in parentheses refer to percentages of patient group.
CABG = coronary artery bypass grafting; MI = myocardial infarction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

There was no difference in event-free survival (Figure 2) and no difference in survival when only the end points of cardiac death or myocardial infarction were considered (Figure 3).

The univariate and multivariate predictors of early revascularization for both groups are listed in Table V. For group 1, the ischemic index, the number of redis-

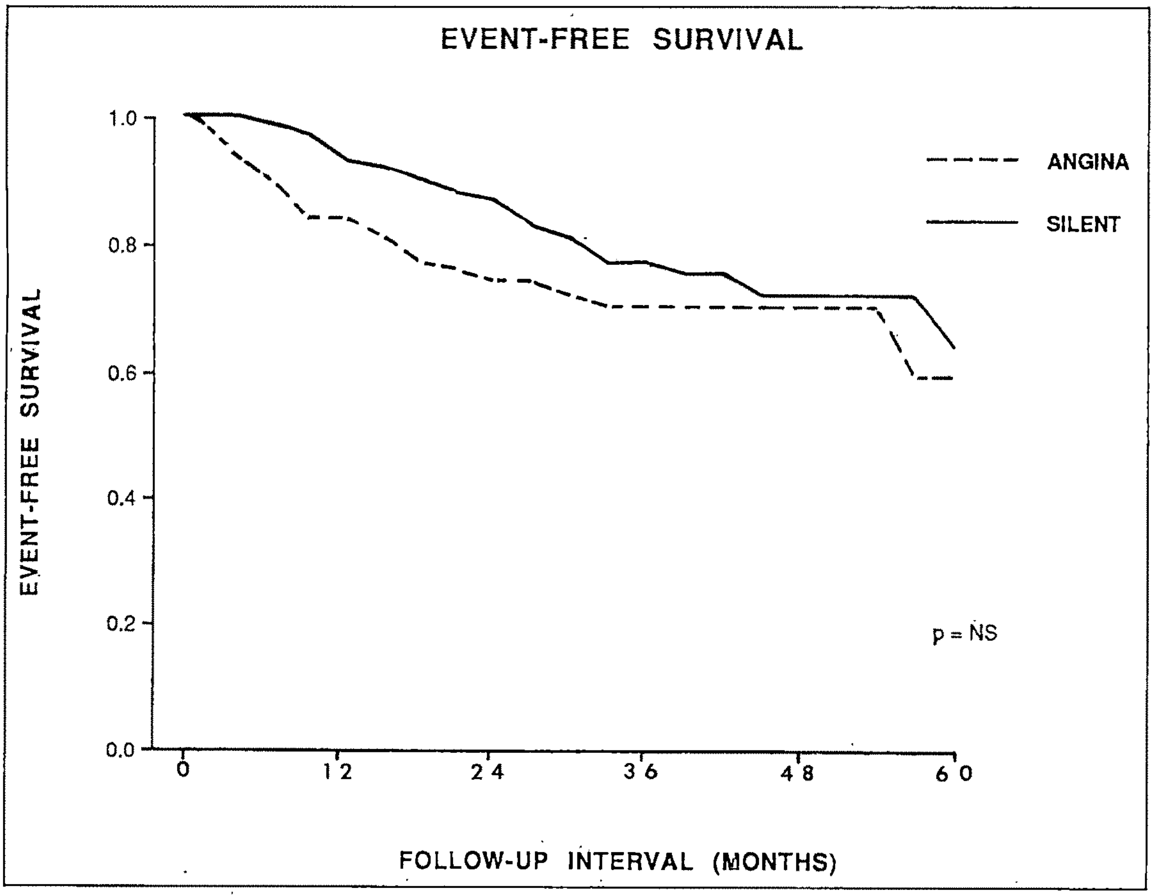

FIGURE 2. Event-free survival of both patient groups. Patients who underwent early revascularization were excluded. Noncardiac deaths were censored at the time of death. NS = not significant.

TABLE V Parameters Predictive of Early Revascularization

	Univariate Predictors		Multivariate Predictors	
Parameter	Chi-Square	p Value	Chi-Square	p Value
Group 1				
ISCH index	14.34	0.0002	10.33	0.0017
Defects (#)	10.52	0.0015		
LVtDIL	5.65	0.0189		
LVDIL	5.49	0.0207		
Group 2				
MPHR (%)	17.70	0.0001	13.85	0.0003
Peak HR	13.41	0.0004		
Peak RPP	9.30	0.0028		
Lung/heart	6.38	0.0128		
LVDIL	5.87	0.0168	6.81	0.0102
ECG	5.62	0.0193	4.94	0.0281

Defects (#) = number of redistributing defects; ECG = positive electrocardiographic response to exercise; HR = heart rate; ISCH = ischemic; Lung/heart = ratio of lung/heart thallium uptake; LVDIL = left ventricular dilatation (transient or fixed); LVtDIL = transient left ventricular dilatation; MPHR (%) = percent maximal predicted heart rate for age achieved during exercise; RPP = rate-pressure product.

tributing defects, the presence of transient left ventricular dilatation and the presence of dilatation both transient and fixed were univariate predictors of early revascularization. Stepwise regression, however, showed that the only independent predictor was the ischemic index. For group 2, the percent maximal predicted heart rate achieved, the peak heart rate, the peak rate pressure product, the lung/heart uptake ratio, the presence of left ventricular dilatation on the stress image, and the presence of electrocardiographic evidence of ischemia predicted early revascularization; the best independent predictor was the percent maximal predicted heart rate achieved.

The various exercise and thallium-201 parameters of the patients whose outcomes were nonfatal myocardial infarction or cardiac death are detailed in Table VI. By multivariate analysis (Table VII), the lung/heart activity ratio and the patient's age best correlated with this outcome in group 1, whereas the presence of fixed left ventricular dilatation and the number of transient thallium-201 defects did so in group 2. Six of 8 cardiac deaths in group 1 and all 4 in group 2 were patients with abnormally increased lung uptake. Eleven of 14 patients in group 1 experiencing nonfatal myocardial infarction or death had left ventricular dilatation as did all of those in group 2.

DISCUSSION

The significance of silent ischemia remains unclear, partly because there is variability in 2 aspects of how silent ischemia is defined. The first is whether to mix

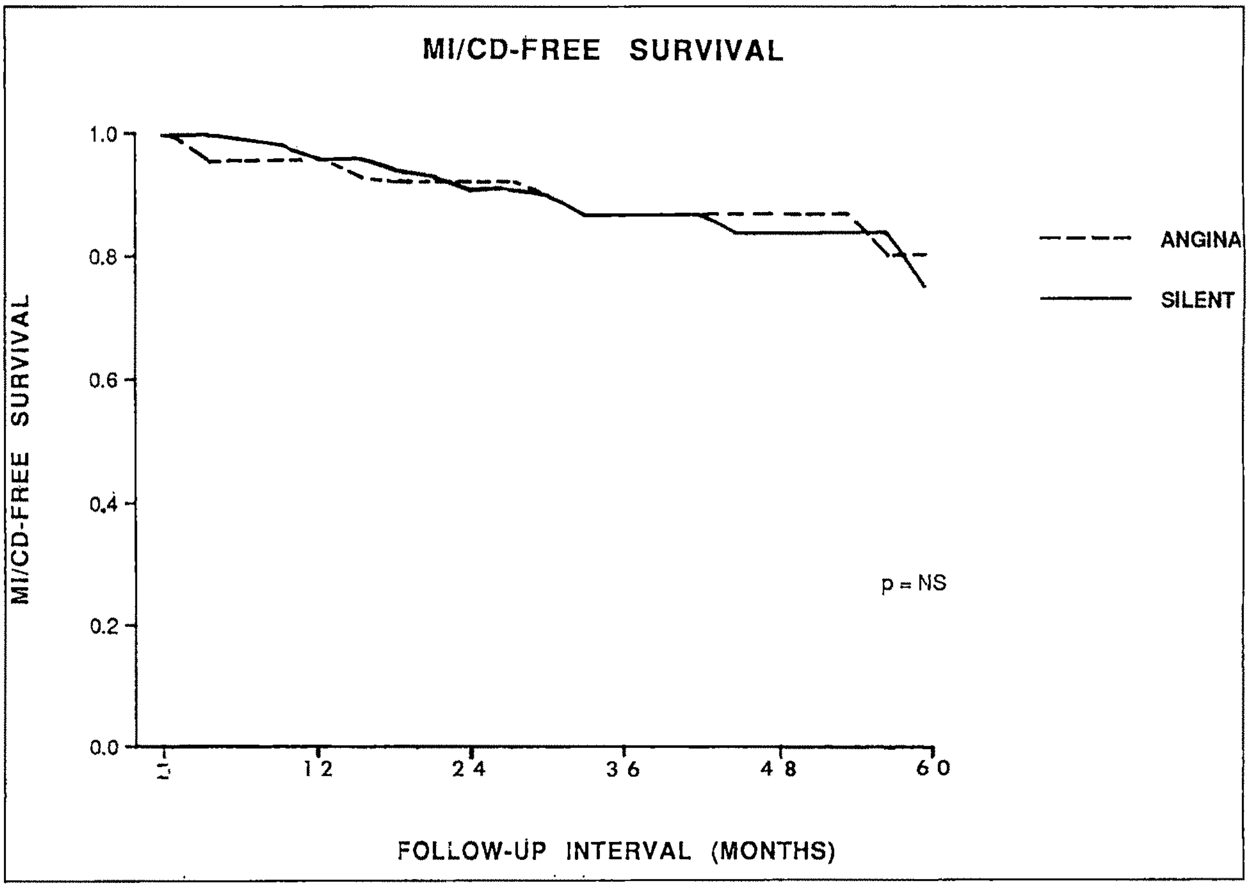

FIGURE 3. Nonfatal myocardial infarction (MI) and cardiac death (CD)–free survival. Patients who underwent early revascularization were excluded. Other revascularization patients were censored at the time of their procedure. Noncardiac deaths were censored at the time of death. NS = not significant.

TABLE VI Exercise and Thallium-201 Variables of Groups 1 and 2

Pt. No.	MI/ CD	Time Event (mos)	Age (yr)	βB	Ex. Time (min)	METs	MPHR (%)	PHR (beats/ min)	Peak RPP/ 1,000	BP	ECG	No. of TIRd	WRST DFCT	II	LU	L/H Ratio	LVDIL
Patients Whose Outcome Was Nonfatal Myocardial Infarction or Cardiac Death: Group 1 (silent ischemia)																	
1	MI	10	56	+	7.0	9.6	93	158	39.5	+	I	4	1	1.8	+	0.49	T
2	MI	7	59	0	4.3	6.8	67	112	15.7	+	0	4	0	1.5	+	0.63	F
3	MI	12	63	0	8.0	9.6	90	150	33.0	+	+	5	1	1.5	+	0.43	0
4	MI	6	66	0	4.3	6.8	66	107	13.9	0	+	4	0	1.6	+	0.44	T
5	MI	20	75	0	9.5	6.8	92	144	31.1	+	I	2	3	0.4	0	0.31	F
6	MI	10	75	0	6.8	6.8	90	140	19.0	0	+	3	2	0.8	0	0.37	T
7	CD	76	57	0	3.0	4.8	71	120	11.4	0	0	2	1	1.1	+	0.46	0
8	CD	60	61	0	11.0	6.8	84	140	19.6	0	0	2	2	0.5	+	0.53	T
9	CD	43	63	+	8.0	9.6	63	105	17.9	+	0	2	3	0.4	+	0.59	F
10	CD	23	62	+	9.0	9.6	73	122	19.0	+	I	1	1	0.8	+	0.67	T
11	CD	29	64	+	6.0	6.8	75	144	21.1	+	+	5	1	1.3	0	0.35	0
12	CD	32	71	+	4.3	6.8	67	107	20.3	0	+	2	2	0.6	+	0.61	T
13	CD	18	73	0	5.0	2.0	91	144	30.2	+	0	4	1	1.0	0	0.31	T
14	CD	16	74	0	5.3	6.8	76	120	15.0	0	I	7	0	3.0	+	0.69	F
Mean ± SD*		26 ± 21	66 ±7		6.5 ± 2.3	7.1 ± 2.1	78 ± 11	128 ± 18	21.9 ± 8.3			3.4 ± 1.6	1.3 ± 1.0	1.2 ± 0.7		0.49 ± 0.13	
Patients Whose Outcome Was Nonfatal Myocardial Infarction or Cardiac Death: Group 2 (symptomatic ischemia)																	
1	MI	3	41	+	8.0	6.8	73	132	23.1	+	+	5	1	2.1	+	0.45	T
2	MI	13	53	+	7.0	9.6	87	150	22.2	0	+	4	2	1.3	0	0.35	T
3	MI	0	61	0	4.0	6.8	72	120	22.8	+	I	6	0	3.5	+	0.55	T
4	MI	14	70	0	14.4	9.6	91	145	24.1	+	+	6	1	2.1	+	0.49	T
5	MI	18	72	0	4.0	6.8	77	122	13.4	0	+	6	2	1.6	0	0.24	T
6	MI	1	74	0	8.7	4.8	86	135	10.3	0	I	6	1	2.0	+	0.78	F
7	CD	56	56	+	6.0	6.8	61	103	15.5	+	I	3	3	0.5	+	0.40	F
8	CD	1	67	+	5.0	6.8	80	129	12.9	0	I	5	1	2.0	+	0.59	F
9	CD	28	68	0	6.0	6.8	84	136	24.5	0	I	2	2	0.4	+	0.71	T
10	CD	33	72	0	3.0	4.8	85	135	23.0	0	+	3	0	1.3	+	0.50	T
Mean ± SD†		17 ± 18	63 ± 10		6.6 ± 3.2	6.7 ± 1.6	80 ± 9	131 ± 13	19.2 ± 5.5			4.6 ± 1.5	1.3 ± 1.5	1.7 ± 0.9		0.51 ± 0.16	

*For all p = not significant compared with Group 2.

†For all p = not significant compared with Group 1.

βB = β blockers (+ = present; 0 = absent); BP = blood pressure response to exercise (+ = normal; 0 = abnormal); CD = cardiac death; ECG = electrocardiographic response to exercise (+ = positive; 0 = negative; I = inconclusive); Ex. = exercise; II = ischemic index; L/H = lung/heart uptake; LU = abnormal lung uptake (+ = present; 0 = absent); LVDIL = left ventricular dilatation (T = transient; F = fixed; 0 = no dilatation); METs = metabolic equivalents; MI = myocardial infarction; MPHR (%) = percent maximal predicted heart rate for age achieved; PHR = peak heart rate; RPP = rate-pressure product; SD = standard deviation; Time Event = time between thallium test and event; TIRd = number of redistributing defects; WRST DFCT = stress grade of most severe redistributing defect (0 to 4 scale).

TABLE VII Parameters Predictive of Nonfatal Myocardial Infarction or Cardiac Death

Univariate Predictors			Multivariate Predictors	
Parameter	Chi-Square	p Value	Chi-Square	p Value
		Group 1		
METs	6.88	0.0087		
Lung/heart	5.95	0.0147	9.23	0.0024
BP	4.25	0.0392		
Age	4.14	0.0418	4.38	0.0364
LVDIL	4.05	0.0442		
Ex. time	3.99	0.0458		
		Group 2		
LVfDIL	8.76	0.0031	9.41	0.0022
LVDIL	7.46	0.0063		
BP	6.11	0.0134		
Peak RPP	5.35	0.0208		
ISCH index	4.89	0.0270		
Defects (#)	4.60	0.0320	6.15	0.0131
METs	3.99	0.0458		

LVfDIL = fixed left ventricular dilatation; other abbreviations as in Tables V and VI.

patients who have episodes of both symptomatic and silent ischemia with patients who have "no angina and no anginal equivalent, either by history or on stress testing," the latter considered by some to be "real silent ischemia."[21] More than half (58%) of our patients with silent ischemia had a history of chest pain. We defined silent ischemia as the occurrence of myocardial ischemia without angina during an exercise test. Our results are applicable to many patients in clinical practice, but may not apply to silent ischemia defined differently.

The second aspect is, which laboratory variable defines silent ischemia? Most previous studies have used ST-segment depression.[2,8–10,13] This study uses thallium scintigraphy, shown to be better for the diagnosis of ischemia.[22,23] Our results therefore are valid only if one uses thallium-201 redistribution, and may not apply to silent ischemia defined differently.

Extent and severity of ischemia: We have shown that when matched for age, sex, and peak exercise heart rate, patients having redistributing defects without angina during an exercise test have, by both electrocardiographic and thallium-201 criteria, less ischemia than patients with angina. This is found despite an equivalence of coronary disease in both groups, suggesting that the extent of anatomic disease does not reflect the extent of physiologic ischemia.

Our results differ from numerous studies that have found no difference in the amount of ischemia between patients with silent and symptomatic ischemia.[3–5,7] In these studies, however, the peak exercise work load was consistently greater in patients with silent ischemia, suggesting that they are in fact less ischemic. However, a recent study by Gasperetti et al[6] found no difference in the extent of thallium-201 hypoperfusion despite equivalent exercise levels in their groups. The reason for the discordance in our results may be their inclusion of a large number of patients (60%) with a previous myocardial infarction (20% recent). Our study, limited to outpatients, had only a 31% incidence of previous myocardial infarction (none recent). In the cited study, the difference between the 2 groups in the extent of ischemia was larger for patients without a previous myocardial infarction. A subgroup analysis of our patients showed that the difference in ischemic severity applied only to patients without a previous infarct, showing the important effect of patient selection on outcome.

In addition the cited study, having only 103 patients vs 268 in ours, did show a trend toward less redistributing defects in the silent group. The differences between our groups was small and required a large number of patients to show significance. Nevertheless, the extensive overlap in our patients does suggest that a difference in ischemic severity is only part of the explanation for the difference in symptomatic responses to exercise.

Prognostic implications: In our study, patients with silent ischemia were less likely to undergo an early (≤6 months) elective revascularization procedure. If early revascularization were to be considered a cardiac event, then patients with silent ischemia would have had a better prognosis. However, a revascularization procedure is often the result of a physician's reaction to the test results rather than an adverse event. Although previous studies have counted revascularization after 2 or 3 months as a cardiac event,[5,20,24] in our study we more conservatively chose a 6-month cut-off, but did count as events patients undergoing revascularization because of clinical deterioration. Using the customary 3-month cut-off would not have altered our conclusions. In either case, we found that for the 214 patients not undergoing early elective revascularization, the prognoses in both groups were the same. Importantly, a separate analysis of these patients also showed that patients with silent ischemia had, despite an equivalent exercise work load, less extensive and less severe ischemia than symptomatic patients. It is unclear why these groups with different amounts of ischemia have similar prognoses. Although the difference in ischemia is large enough for statistical significance, it may be too small for clinical significance. Importantly, patients with symptoms are likely to receive more aggressive medical therapy.

Although it has been shown that silent ischemia is prognostically worse than no ischemia,[25–27] studies that have compared the prognosis relative to symptomatic ischemia have reached varying conclusions. Whereas some studies have shown that patients with silent ischemia have a more favorable prognosis,[2,12] others, like ours, have shown no difference.[1,5,8-10] A few studies have shown that patients with silent ischemia have a less favorable prognosis.[3,11] These differences, although partly the result of variations in patient selection, may relate more to how physicians in various institutions view the importance of diagnostic studies, such as thallium stress testing, and how the test results influence their decision to send a patient for revascularization.[28] Breitenbücher et al[11] saw that although symptomatic patients were more likely to undergo revascularization, those with silent ischemia had a higher incidence of subsequent myocardial infarction and cardiac death. In their study, however, only 7% of patients with silent ischemia underwent revascularization compared with 20% in our study. The higher revascularization rate in our patients with silent ischemia probably decreased the number of subsequent cardiac events, equalizing their outcome to that of the symptomatic patients. That the ischemic index was the best predictor of early elective revascularization in our group with silent ischemia suggests that physicians at our institution were greatly influenced by the thallium test results in their decision to send these patients for revascularization. Our results may therefore not apply to institutions that rely more on symptoms and less on thallium-201 image results.

Study limitations: There are several important limitations to this study. The first is that we used planar imaging instead of single-photon emission computed tomographic imaging. Planar imaging is impaired by geometric overlap, although we attempted to account for this in the calculation of the ischemic index. A similar study that did use quantitative single-photon emission computed tomography[7] found no difference in perfusion defect size in silent versus symptomatic ischemia, but included many patients without radionuclide ischemia.

Second, as we only selected patients who could be matched, we did not fully evaluate all patients presenting to our laboratory during this time period. Seventy-one patients with and 277 without angina were excluded because of inability to match.

Third, we selected patients who had their tests over a long time period (1982 to 1988). As there is evidence for a declining thallium specificity over the years,[29] the test year could conceivably have affected physician decisions after thallium-201 imaging, influencing the cardiac event rate. We found, however, that the rate of early elective revascularization did not vary according to the year in which the thallium exercise test was performed.

Finally, conclusions in this study are based on a retrospective review of stress data, including the patient's symptoms during the test. Although the data were analyzed carefully to determine whether symptoms were anginal, subjective judgment was required in many cases. Approximately 12 physicians performed these tests over the 6-year period, adding further subjectivity. Prospectively obtained data would certainly have strengthened the conclusions of this study. One must also consider that dyspnea may be an anginal equivalent, but distinguishing dyspnea due to ischemia from that due to deconditioning or fatigue during a stress test is difficult.

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Experience with Low-Dose Intracoronary Recombinant Tissue-Type Plasminogen Activator for Nonacute Total Occlusions Before Percutaneous Transluminal Coronary Angioplasty

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The primary success rate for angioplasty of total occlusions is significantly worse than for subtotal lesions. Pharmacologic recanalization of total occlusions before angioplasty has the potential to improve the primary success rate. To determine the ability of recombinant tissue-type plasminogen activator (rt-PA) to recanalize occlusive thrombi before elective percutaneous transluminal coronary angioplasty, 12 patients with total occlusions, 100% obstruction and Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow, and 5 with functional total occlusions, severe stenoses and TIMI grade 1 flow received an intracoronary infusion of rt-PA. The first 10 patients received 0.2 mg/min for 90 minutes, and the next 7 patients received 0.4 mg/min for 60 minutes. Flow improved by $\geq$1 TIMI grade in 11 patients. Mean TIMI flow improved from 0.3 ± 0.5 to 1.5 ± 1.2 ($p < 0.0001$). There was a significant improvement in severity of stenosis after rt-PA infusion by both digital caliper (99 ± 2 vs 84 ± 16%; $p < 0.0001$) and quantitative videodensitometric area assessment (99 ± 3 vs 94 ± 6%; $p < 0.004$). Angioplasty was successful in 16 of 17 patients (94%). There were 2 out-of-laboratory abrupt closures at 4 days; both were medically treated and 1 had a small myocardial infarction. Only 1 patient had a bleeding complication significant enough to need a transfusion. It is concluded that low-dose intracoronary rt-PA is effective at lysing thrombi <3 weeks old. This approach warrants further investigation since it may significantly improve the primary success rate of percutaneous transluminal coronary angioplasty in patients with occlusive thrombus.

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Coronary angioplasty of chronic total occlusions has a lower primary success rate (50 to 70%) than that of subtotal occlusions (approximately 90%).[1-7] The reasons for this relatively low primary success are multiple, but the major problem common to every case is "blindly" steering the guidewire through the total obstruction. A recent report from the Percutaneous Transluminal Coronary Angioplasty[8] registry confirms that failure to successfully dilate a total occlusion is due to the inability to pass the wire 81% of the time.[8] Clearly, if flow could be reestablished before angioplasty, the ability to place the guidewire across the lesion would improve substantially.

The pathophysiology of acute myocardial infarction involves the formation of an occlusive thrombus, which is the event that converts a subtotal to a total occlusion in most cases.[9-11] Theoretically, the fibrin component of the thrombus should be susceptible to thrombolytic therapy until organization is complete. Experience with peripheral occlusions suggests that it is possible to lyse nonacute thrombi with local infusion of recombinant tissue-type plasminogen activator (rt-PA).[12] Accordingly, we tested the hypothesis that selective administration of low-dose rt-PA at the site of a nonacute total coronary obstruction will lyse the fibrin component of the obstruction and reestablish blood flow.

METHODS

The study group consisted of 17 patients referred to Boston University Medical Center from January 1989 to December 1990 for angioplasty of a total or functional total occlusion who met the following inclusion criteria: Patients with a total occlusion (n = 12), 100%

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TABLE I Clinical Characteristics, Angiographic Data and Outcome of 17 Study Patients

Case No.	Age (y) & Sex	Indication for PTCA	Duration of Symptoms (days)	VD/ Culprit	Cath–PTCA Interval (days)	TIMI Flow (before/after)	Complications
1	66M	PIA	1	SVD/right	1	1/3	Embolus
2	45M	SEMI	2	MVD/LAD	2	0/2	
3	43M	UA	3	SVD/right	3	0/2	GB, AC (4 days after PTCA)
4	56M	UA	4	SVD/right	7	1/3	
5	67M	SEMI/PIA	5	SVD/right	2	0/3	GB
6	49M	SEMI/PIA	5	SVD/LC	1	0/0	
7	45M	SEMI	6	SVD/right	1	1/3	GB
8	58M	SEMI/PIA	8	SVD/right	2	0/2	Hematoma, AC (4 days after PTCA), +MI
9	41M	UA	9	SVD/LAD	4	1/3	
10	31M	PIA	9	SVD/right	0	0/0.5	GB
11	52M	PIA	10	SVD/right	5	0/0.5	Embolus
12	65M	UA	12	SVD/LC	0	1/2	
13	42M	PIA	12	SVD/LC	0	0/1	
14	54F	PIA	15	SVD/right	12	0/1	
15	66F	SEMI	22	MVD/LAD	4	0/0	Hematoma
16	53M	UA	32	SVD/right	0	0/0	
17	62F	PIA	90	MVD/right	30	0/0	Access site pseudoaneurysm

AC = abrupt closure; Cath = diagnostic catheterization; GB = gingival bleeding; LAD = left anterior descending; LC = left circumflex; MI = myocardial infarction; MVD = multivessel disease; PIA = postinfarction angina; PTCA = percutaneous transluminal coronary angioplasty; SEMI = subendocardial myocardial infarction; SVD = single vessel disease; TIMI = Thrombolysis in Myocardial Infarction; UA = unstable angina; VD = vessel disease.

stenosis and Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow had to have clinical evidence that the obstruction was <3 months old. Patients with a functional total occlusion (n = 5), severe stenosis and TIMI grade 1 flow had to have angiographic evidence of definite thrombus. Exclusion criteria consisted of any contraindication to thrombolytic therapy, including history of bleeding diathesis, stroke, trauma or major surgery within 3 months, poorly controlled hypertension or a reading >180/110 mm Hg in the catheterization laboratory, or a platelet count <100,000/mm. Participation in an ongoing randomized protocol or the need for emergent angioplasty were also reasons for exclusion. Patients who recently underwent cardiac catheterization were considered candidates if the access site was well-healed without a significant hematoma, so that evaluation and compression could be performed if needed.

Angiography protocol: All patients were receiving aspirin, persantine and a calcium antagonist ≥12 hours before angioplasty and were premedicated with valium and benadryl The procedure was performed using the standard Seldinger technique with both arterial and venous access. A temporary pacing catheter was placed in the pulmonary artery for pacing capability and pressure monitoring. Patients received a standard bolus of 100 U/kg of heparin and a maintenance infusion of 1,000 U/hr. The activated clotting time was monitored frequently, and infusion of heparin was adjusted to yield an activated clotting time of 300 to 400 seconds. All patients received nitroglycerin before angiography. Standard orthogonal views were obtained before angioplasty. An angioplasty catheter was placed just proximal to the occlusion, and the guidewire was removed to allow selective infusion of rt-PA. If the occlusion was too proximal to permit stable placement of the angioplasty catheter, the drug was infused through the guide. Cinecoronary angiography was performed every 30 minutes during infusion. After infusion was completed, orthogonal views were repeated. The angioplasty then proceeded in standard fashion.

Both coronary perfusion and percent stenosis were assessed before and after rt-PA, and after angioplasty by 2 angiographers. Perfusion was assessed using the TIMI grading system[11] with 1 modification. If there was a definite increase in contrast penetration into the total occlusion without anterograde flow, a value of 0.5 was assigned. Severity of stenosis was assessed at end-diastole with orthogonal views when possible or with the 1 best view when foreshortening occurred, by both digital calipers and videodensitometric area (Artrek program) using digital angiography.

Drug infusion: The dose of intracoronary rt-PA was calculated to yield a high concentration at the site of the thrombus without reaching a significant systemic level. The usual intravenous dose of rt-PA yields approximately a 2.0 μg/ml plasma concentration at 90 minutes.[13] Using standard assumptions for hematocrit (40%) and coronary blood flow (200 ml/min), an intracoronary infusion of approximately 0.2 mg/min is needed to achieve this concentration at the site of the obstruction. Most recanalization occurs by 90 minutes with the systemic administration of rt-PA.[14] Therefore, for the first 10 patients the intracoronary regimen was 0.2 mg/min for 90 minutes, including a 0.5 mg bolus, for a total dose of 18.5 mg. In an attempt to decrease

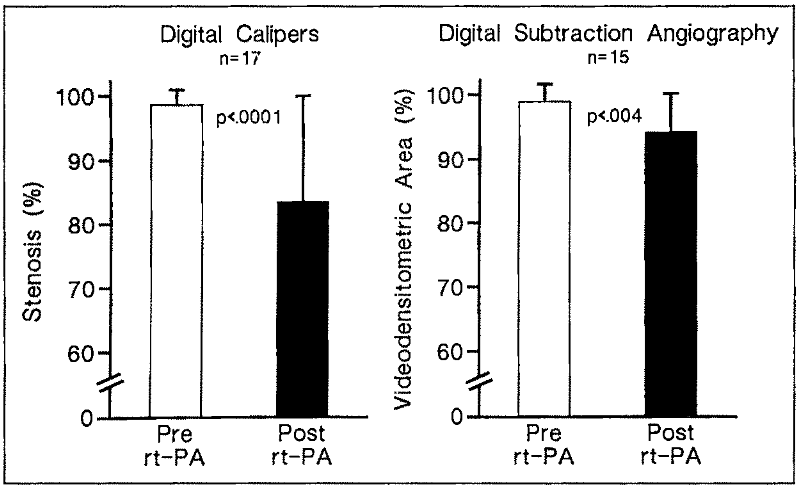

FIGURE 1. Stenosis assessed by both digital calipers and quantitative digital angiography before (Pre) and after (Post) recombinant tissue-type plasminogen activator (rt-PA). Two patients did not have digital angiograms available for analysis; both responded to rt-PA.

time to reperfusion, the last 7 patients received a dose of 0.4 mg/min for 60 minutes, and a 1.0 mg bolus, for a total dose of 25 mg.

Hematologic parameters: Fibrinogen levels and platelet function test using a Biodata aggregometer were obtained before and immediately after rt-PA.

Statistical analysis: Groups of patients were compared using chi-square analysis for categorical data, and Student's *t* test for continuous data.

RESULTS

Patient characteristics: Clinical characteristics of the 17 study patients are listed in Table I. Patients are arranged according to clinically estimated age of intracoronary thrombus, which was based on the date of their recent infarction or change in anginal symptoms.

Thirteen patients had a diagnostic cardiac catheterization within 1 month of their angioplasty. Nine of these patients had angioplasty through a new access site, and 4 had sheath exchanges and used the same access site.

Angiographic data: Extent of coronary disease, the culprit vessel and TIMI grade coronary flow are listed in Table I. Twelve of 17 (70.6%) patients had a complete occlusion of 100%. Functional total occlusion with severe (≥95%) stenosis with TIMI grade 1 flow and definite thrombus, was present in 5 of 17 (29.4%) patients. Mean left ventricular ejection fraction was normal (56.4%; n = 13). Collaterals to the obstructed vessel were present in 14 of 17 (82.3%) patients.

Stenosis severity after rt-PA is shown in Figure 1. There was significant improvement in stenosis severity after infusion of rt-PA by both digital caliper (99 ± 2 vs 84 ± 16; p <0.0001) and videodensitometric area assessment (99 ± 3 vs 94 ± 6; p <0.004).

The effect of rt-PA on perfusion grade is illustrated in Figure 2. Mean TIMI flow improved from 0.3 ± 0.5 to 1.5 ± 1.2 (p <0.0001). Eleven patients had increases of ≥1 TIMI grade. Two of the arteries that remained totally occluded had evidence of partial resolution of thrombus (i.e., increased penetration of contrast without recanalization [TIMI grade 0.5]), and 4 had no response.

Clinical age of thrombus influenced the likelihood of successful thrombolysis. In 12 of 14 patients with occlusion durations of 1 to 21 days there was definite evidence of thrombolysis, whereas none of the 3 patients with an occlusion duration >21 days had any evidence of thrombolysis (p = 0.02).

Time to reperfusion appeared to be more rapid with the higher dose of rt-PA. With the 0.2 mg/min dose none of the total occlusions <21 days old had evidence of reperfusion at 30 minutes, 2 of 5 began to reperfuse at 60 minutes, and 1 of 5 began at 90 minutes. With the 0.4 mg/min dose, 4 of 5 total occlusions <21 days old had evidence of reperfusion that occurred at 30 minutes in 3 patients and at 90 minutes in 1.

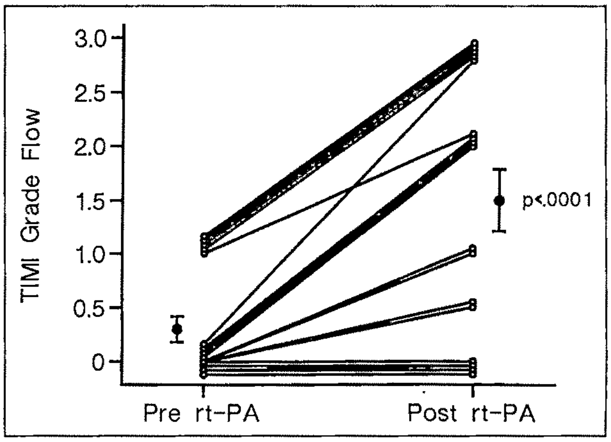

FIGURE 2. Perfusion grade before (Pre) and after (Post) recombinant tissue-type plasminogen activator (rt-PA) (mean ± standard error). TIMI = Thrombolysis in Myocardial Infarction.

Angioplasty was successful in 16 of 17 patients (94%). Severity of stenosis was reduced to 30 ± 20%, and perfusion was normal in all patients with successful dilations. The 1 unsuccessful angioplasty occurred in a patient whose total occlusion was 22 days old and did not respond to intracoronary rt-PA. The angioplasty wire could not be passed across the total occlusion.

Hematologic parameters: There was no change in fibrinogen after rt-PA (before 392 ± 143 vs after 387 ± 116 mg/dl). A trend toward increased platelet aggregability occurred after rt-PA in response to collagen (62 ± 20 vs 65 ± 17%), ristocetin (75 ± 12 vs 81 ± 13%) and epinephrine (34 ± 12 vs 40 ± 13%). Response to adenosine diphosphate was significantly increased (52 ± 20 vs 67 ± 12%; $p = 0.03$). Response to arachidonic acid, reflecting pretreatment with aspirin, was low and unchanged after rt-PA (15 ± 13 vs 12 ± 7%).

Complications: All patients were observed for the presence of bleeding, and individual events are listed in Table I. Minor gingival bleeding occurred in 4 of 17 patients (23%). Three hematomas were seen; 2 occurred, during the infusion, at an arterial access site for catheterization performed 2 and 4 days earlier, respectively. Sheath removal in each case was complicated by a small hematoma that increased in size after rt-PA. None of the other 7 patients undergoing catheterization 1 to 12 days earlier developed bleeding from their recent arterial puncture site. The third hematoma occurred after sheath removal the day after angioplasty, and was complicated by pseudoaneurysm formation and the need for transfusion after repair.

Two patients had angiographically evident emboli. One resolved after administration of an additional 10 mg of rt-PA. The other resolved spontaneously and was asymptomatic.

Out-of-laboratory abrupt closure occurred in 2 patients after discontinuation of heparin 4 days after angioplasty. Thrombolysis exposed a 2 cm long, type 3 lesion in 1 patient who was treated medically and had a small myocardial infarction with 560 U/liter of creatine kinase. Repeat angioplasty was attempted in the other patient, but was unsuccessful and uncomplicated.

DISCUSSION

The goal of this study was to test the hypothesis that administration of a low dose of rt-PA at the site of a nonacute total coronary occlusion would lyse the fibrin component of the obstruction and restore anterograde flow. The results document that intracoronary rt-PA is capable of lysing occlusive thrombi up to 3 weeks old. This was accomplished with a relatively high success rate, as indicated by significant reduction in severity of stenosis and by improvement in anterograde flow.

Our results were obtained with a low dose of rt-PA that decreases the likelihood of a serious complication such as intracranial hemorrhage.[15] Even at the low doses used there was some evidence of systemic effect, most often manifested by gingival bleeding. However, the systemic effects appear to be mild, because most patients with recent arterial punctures did not develop any bleeding. The 2 patients who did bleed from their recent arterial puncture site had moderate hematomas not needing transfusion. Of note, both patients had small hematomas before administration of rt-PA at the site of their previous catheterization. Thus, it appears that any hematoma increases the risk of bleeding.

Although there was some evidence of systemic effect, there was no evidence of fibrinogen depletion. Interestingly, there was evidence of platelet activation. This phenomenon has recently been studied by Rudd et al.[16] Platelet activation appears to occur frequently shortly after administration of thrombolytic agents, but within hours actually results in antiaggregatory effects. The degree of platelet activation present in our patients did not appear to have clinical significance, because the primary success rate was 94%, and both episodes of abrupt closure occurred 4 days after angioplasty when heparin was stopped.

A 12% (2 of 17) abrupt closure rate is of concern. An increased incidence of both acute and delayed abrupt closures has been noted when thrombus is present and during angioplasty of total occlusions.[2,17] One would hope that pretreatment with rt-PA would decrease the bulk of thrombus and therefore decrease the likelihood of abrupt closure, but a larger series of patients is needed to address this question adequately. An observation worth noting is that pretreatment with rt-PA of 1 of the patients that abruptly closed, exposed a >2 cm long type 3 lesion. Ordinarily, type 3 lesions are not accepted for percutaneous transluminal coronary angioplasty (PTCA), because of the high risk of abrupt closure. By definition, one does not know the morphology of a total occlusion before angioplasty and therefore cannot avoid the higher risk lesions. This may partially explain the lower primary success rate and higher abrupt closure rate associated with total occlusions.

Whether pretreatment of total occlusions with rt-PA before PTCA will improve the primary success rate needs further evaluation. It has been well-established that total occlusions, even if relatively recent, as in our study, have a lower success rate than subtotal occlusions.[3–7] An adjuvant therapy that could restore anterograde flow should improve the likelihood of primary success. It is intriguing that the primary success rate in our group of patients was 94%, a rate associated with subtotal occlusions.

One must also be cautious of the potential harm that pretreatment with rt-PA may cause. Recent studies have established that PTCA for an acute myocardial infarction after thrombolytic therapy is associated with more complications than is delayed angioplasty.[18] The hypercoaguable state that is present during acute infarction, especially at the site of the lesion, may be responsible for these results, but it is also possible that thrombolysis may cause hemorrhage in the wall of the dilated plaque, and actually increase the incidence of abrupt closure and serious complications. Concern regarding the risk of intracranial hemorrhage is always present when administering a thrombolytic agent. Although there was a trend toward shorter time to reperfusion and toward increased efficacy with the higher, 0.4 mg/min dose of rt-PA used in this study, higher doses would approach levels known to be associated with a 0.5 to 1.0% incidence of intracranial hemorrhage. The risk-benefit ratio remains favorable for acute myocardial infarction, but not for elective PTCA.

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Comparison of Angiographic Findings and Demographic Variables in Patients with Coronary Artery Disease Presenting with Acute Pulmonary Edema Versus Those Presenting with Chest Pain

Susan P. Graham, MD, and George W. Vetrovec, MD

One hundred nineteen patients admitted to the coronary care unit with pulmonary edema were retrospectively reviewed to identify the demographic characteristics and underlying cardiac disorders of this population. The patients with pulmonary edema were compared with 119 patients admitted to the coronary care unit with chest pain. Cardiac catheterization in 71 patients with pulmonary edema and 93 with chest pain showed left main and 3-vessel coronary artery diseases to be equally common in both groups, although anginal pain was infrequent in patients with pulmonary edema (n = 28, 24%). Left ventricular function was reduced in the patients with pulmonary edema compared with those with chest pain (mean ejection fraction 42 vs 59%; p <0.001). More patients with pulmonary edema were black, and had diabetes and preexisting hypertension than those with chest pain. The results of cardiac catheterization were the same for black and white patients with pulmonary edema. In conclusion, patients with pulmonary edema have a high incidence of cardiac disease, and pulmonary edema may be 1 manifestation of silent myocardial ischemia. Important demographic differences exist between patients admitted with pulmonary edema and those who present with chest pain.

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Pulmonary edema is a dramatic manifestation of cardiac dysfunction. Patients presenting with pulmonary edema have an increase in cardiac events and death, leading to a poor short- and long-term prognosis.[1-6] Although some characteristics of these patients have been described,[7-12] no comprehensive evaluation of underlying cardiac conditions is available. This study describes the demographic and angiographic findings of patients presenting with pulmonary edema compared with those of a matched group presenting with chest pain but without pulmonary edema.

METHODS

Patient population: During 1 calendar year, 1,400 patients were admitted to the coronary care unit of the Medical College of Virginia; 141 patients (9.4%) had a primary diagnosis of pulmonary edema. The diagnosis was established by the admitting physician and was documented by: (1) history of new or worsened and persistent shortness of breath, nocturnal dyspnea or orthopnea; (2) physical examination demonstrating rales, S3 or a respiratory rate >16 breaths/minute; and (3) supporting laboratory studies showing hypoxia, cardiomegaly or pulmonary congestion on a chest radiograph. Nine patients awaiting cardiac transplantation and 13 with unavailable medical records were excluded, leaving 119 individuals for evaluation.

A comparison group of 139 patients with chest pain but without pulmonary edema were matched to those with pulmonary edema by the day and hour of admission to the coronary care unit; charts were available in 119 (86%) of these patients.

Data acquisition: Information was obtained from the medical records regarding: (1) history of hypertension, diabetes or typical anginal chest pain (anginal chest pain was defined as midsternal chest pressure occurring with exertion, and relieved by rest or nitroglycerin, with or without radiation to the neck or arms, diaphoresis, nausea or dyspnea); (2) myocardial infarction documented by new Q waves or ST-T wave changes on the electrocardiogram and by elevation of cardiac enzymes; and (3) time of arrival in the emergency room for patients with pulmonary edema.

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Cardiac catheterization: Cardiac catheterization was performed at the discretion of the attending cardiologist when the patient was clinically stable.

Right heart pressures were recorded before angiography. Elevated pressures were defined as pulmonary artery systolic pressures >30 mm Hg or pulmonary arterial wedge pressures >14 mm Hg, or both.

Selective coronary arteriography was performed in multiple projections using the Judkins technique. "Significant" coronary artery disease (CAD) was defined as ≥70% diameter stenosis. Significant valvular insufficiency was defined as ≥ +2 to +3. Significant valvular stenoses were defined as aortic valve areas ≤1.0 cm^2 and mitral valve areas ≤1.4 cm^2. Ejection fraction was calculated from the ventriculogram in the right anterior oblique projection. Cardiomyopathy was defined as an ejection fraction <40% with normal coronary arteries.

Of the 119 patients with pulmonary edema, 71 (60%) underwent cardiac catheterizations; 38 during the index admission, 33 during a preceding admission and 4 during a subsequent admission (average: within 4.5 months of index admission). Ninety-three (86%) of the 119 patients with chest pain had catheterization; 73 during the index admission and 20 during a previous admission.

Statistics: Data are expressed as mean ± standard error of the mean. Unpaired *t* tests and chi-square analyses were used for statistical comparisons between the groups. Results were considered significant for p ≤0.05.

RESULTS

Demographic data: Demographic characteristics of the populations with pulmonary edema and chest pain are listed in Table I and Figure 1. Patients with pulmonary edema undergoing cardiac catheterization were not statistically different from the entire group with pulmonary edema (Table I). More of the patients with pulmonary edema were older and black, and had antecedent hypertension and diabetes than the patients with chest pain. Cardiovascular risk factors were similar for black and white patients (Figure 1). The incidence of myocardial infarction during the index admission was the same for both groups, but only 24% of the group with pulmonary edema had past history of anginal pain.

TABLE I Demographic Data

	Pulmonary Edema (n = 119)	Pulmonary Edema with Catheterization* (n = 71)	Chest Pain (n = 119)	p Value†
Age (yr, mean ±SEM)	63 ± 1	62 ± 1	57 ± 1	<0.001
Age range (yr)	22–88	26–83	29–91	
Men	58 (49%)	41 (58%)	72 (60%)	<0.10
White	48 (40%)	34 (48%)	72 (60%)	<0.01
Hypertension	68 (57%)	38 (54%)	50 (42%)	<0.05
Diabetes	39 (33%)	23 (33%)	14 (12%)	0.001
Myocardial infarction	21 (18%)	13 (18%)	27 (23%)	NS
Chest pain	28 (24%)	13 (18%)	119 (100%)	

*p = NS for pulmonary edema versus pulmonary edema with catheterization in all categories; †pulmonary edema versus chest pain.
NS = not significant; SEM = standard error of the mean.

Cardiac catheterization: Table II lists the results of cardiac catheterization. Two thirds of the patients with pulmonary edema had significant CAD (35 [49%] with 3-vessel disease, 7 [10%] of whom had left main disease). For the patients with chest pain, 78 (84%) had CAD, including 33 (35%) with 3-vessel disease. Of the 23 (32%) patients with pulmonary edema without CAD, only 5 had normal catheterization, the remaining having dilated cardiomyopathy (7), valvular disease (8) or elevated right heart pressures (3). Of the patients with chest pain without CAD, 12 had normal catheterization, 1 had valvular disease and 2 had elevated right heart pressures. The patients without CAD were excluded from further analysis.

Mean ejection fraction of the group with pulmonary edema (42%) was significantly lower than that of the

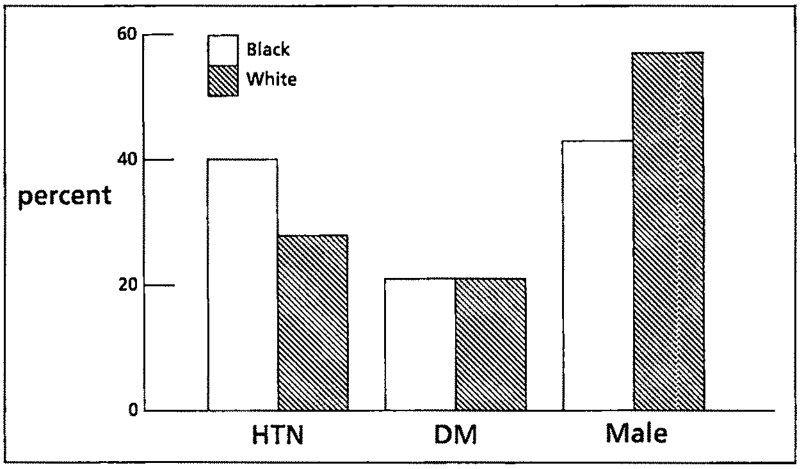

FIGURE 1. Incidence of diabetes (DM), hypertension (HTN) and male gender in black (n = 71) and white (n = 48) patients. p = not significant for all comparisons.

TABLE II Cardiac Catheterization

	Pulmonary Edema (n = 71)	Chest Pain (n = 93)	p Value
Ejection fraction			
(%, mean ± SEM)	42 ± 2	59 ± 1	<0.001
Range (%)	15–75	10–83	
Right heart pressures			
Normal	48 (68%)	78 (84%)	<0.02
Increased	23 (32%)	15 (16%)	<0.02
Coronary disease (total)	48 (68%)	78 (84%)	
Left main	7 (10%)	4 (4%)	NS
3-vessel*	35 (49%)	33 (35%)	NS
2-vessel	7 (10%)	21 (22%)	<0.10
1-vessel	6 (8%)	24 (26%)	<0.01
Not significant	23 (32%)†	15 (16%)‡	<0.02

*Includes patients with left main disease; †5 normal, 8 valvular disease, 7 cardiomyopathy and 3 elevated pressures; ‡12 normal, 1 valvular disease and 2 elevated pressures.
Abbreviations as in Table I.

TABLE III Cardiac Catheterization by Race: Pulmonary Edema Group (n = 71)

	Black (n = 38)	White (n = 33)	p Value
Ejection fraction			
(%, mean ± SEM)	40 ± 3	41 ± 3	NS
Range (%)	15–77	19–75	
Coronary disease			
Left main	2 (5%)	2 (6%)	NS
3-vessel*	17 (45%)	19 (58%)	NS
2-vessel	2 (5%)	4 (12%)	NS
1-vessel	2 (5%)	3 (9%)	NS

*Includes patients with left main disease.
Abbreviations as in Table I.

group with chest pain (59%) (p <0.001). Fifty (70%) of the patients with pulmonary edema and 21 (22%) of those with chest pain had ejection fractions <50%.

Despite a greater number of black patients in the group with pulmonary edema, there was no difference in the results of cardiac catheterization when analyzed by race (Table III).

Time of presentation with pulmonary edema: Figure 2 demonstrates the hour of the day during which 89 patients with pulmonary edema presented to the emergency room.

DISCUSSION

Pulmonary edema with or without myocardial infarction has a poor prognosis, with an increase in immediate and long-term morbid events.[1-7] Clark et al[2] reported a 60% two-year mortality in 56 patients with pulmonary edema with coronary disease, but without valve disease, cardiomyopathy or myocardial infarction. Other studies[1] have described a hospital mortality of 17%[6] with a 1-year mortality of 43%.

The results of this study, showing the high incidence and severity of CAD, and depressed left ventricular function in patients with pulmonary edema, may explain the poor outcome. Extensive CAD and left ventricular dysfunction are important predictors of future cardiac mortality, with improvement in survival and symptoms achieved by revascularization and valve repair.[9,14-21]

Seventy-six percent of the patients with pulmonary edema had no prior history of chest pain, although 68% of those catheterized had significant underlying CAD. This suggests that pulmonary edema may be 1 manifestation of silent ischemia. Diagnostic catheterization in addition to noninvasive studies that elucidate ventricular function and valve disorders should be considered in this population.

Patients with pulmonary edema were older than those with chest pain. The absence of angina may be due to a decline in physical activity or an increase in the anginal threshold with aging.[22] Although symptoms may change in the elderly, both the cumulative risks of CAD and the mortality associated with pulmonary edema increase with age.[1,2] The operative risk for heart surgery increases in patients aged >70 years, but it must be weighed against the predicted poor outcome with conservative management.

In this study, a large proportion of black patients (60%) underwent cardiac catheterization. In the Coronary Artery Surgery Study (CASS)[23] blacks constituted only 2.4% of the study population. The CASS investigators reported that white patients had more severe CAD despite more cardiovascular risk factors in

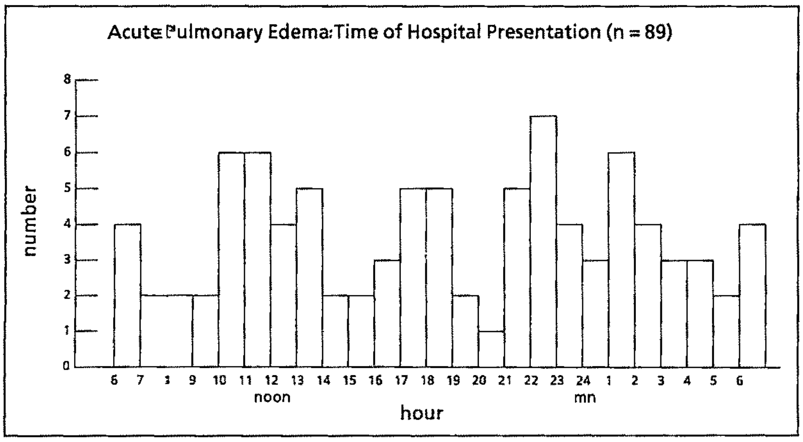

FIGURE 2. Admission to the emergency room for patients with pulmonary edema by hour of the day. mn = midnight.

black patients.[23] In contrast, we found no difference between black and white patients with regard to cardiovascular risk factors or the results of cardiac catheterization (Figure 1, Table III).

Finally, we reviewed the time of admission to the emergency room for patients with pulmonary edema to see if there was a circadian variation in presentation. Patients arrived in the emergency room throughout the 24-hour day. There was a trend toward more admissions during the late morning (1000 to 1300 hours), late afternoon (1500 to 1800 hours), and nighttime (2200 to 0100 hours), but there were too few patients in each time period for meaningful statistical comparison. Other investigators have reported an increase in morning events in patients with ischemia[24,25] and sudden cardiac death.[26] More episodes of silent myocardial ischemia,[27] pain at rest,[28] myocardial infarction,[29] and ventricular tachycardia[30] have been seen in late afternoon. Pulmonary edema in the late evening may arise for several reasons. First, ischemia may worsen or the ischemic threshold may decrease at night.[28,31,32] Second, the serum level of morning medications may decline. Third, fluid retained during daytime activity may redistribute centrally. Finally, patients performing shift work may have altered circadian rhythms (none of our patients worked during the night shift). The contribution of each of these factors cannot be determined in this study, but would be interesting to pursue in a future investigation.

One limitation of this study is that demographic factors may have influenced our results. Cardiac catheterization may be recommended more often for younger individuals and for those with classic anginal symptoms. The Medical College of Virginia is both a primary city hospital and a tertiary referral institution. The population with pulmonary edema may be more representative of local city inhabitants who use the hospital as their primary source of medical care. Conversely, more of the patients with chest pain had typical ischemic symptoms, prompting their referral for invasive procedures.

Conclusion: This study demonstrates a high incidence of significant cardiac abnormalities in patients with pulmonary edema who undergo cardiac catheterization. Despite infrequent history of typical angina, 48 patients (68%) who underwent catheterization had significant CAD. Optimal management of patients presenting with pulmonary edema requires identification of precipitating factors. Future studies will be needed to assess the outcome of more aggressive diagnostic and revascularization efforts in this population.

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Significance of Signal-Averaged P-Wave Changes During Exercise in Patients with Coronary Artery Disease and Correlation with Angiographic Findings

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The maximal P-wave duration in all time-aligned leads, and the maximal P-wave amplitude in leads V_5 and V_6 were measured on a 12-lead, signal-averaged electrocardiogram during the recovery period of an exercise stress test (EST). The study group consisted of 75 patients with coronary artery disease (CAD) documented by ≥50% diameter stenosis in 1 or more arteries and a control group of 47 subjects, 15 of them young volunteers and 32 with no or minimal coronary atherosclerosis and normal left ventricular function. All subjects underwent a symptom limited EST, with use of the Ellestad protocol. Signal-averaged P waves recorded before exercise, and for the first 6 minutes in recovery were measured using a 5× magnifier. The mean P duration before exercise in the control group was 107 ± 16 ms (± 1 standard deviation) and 111 ± 15 ms at the third minute of recovery, ($p < 0.001$). In patients with CAD it was 112 ± 12 and 129 ± 19 ms (± 1 standard deviation), $p < 0.001$, respectively. Differences in P-wave duration were found to be statistically significant ($p < 0.001$) throughout recovery in the group with CAD when compared with control and maximal values at the third minute. The increase in P-wave duration (≥20 ms) was used as an additional parameter to exercise-induced ST-segment depression, ST elevation, or anginal pain for the test interpretation. The sensitivity increased from 57 to 75% and the specificity decreased from 85 to 77%. It is concluded that the measurement of the P-wave duration during recovery adds diagnostic power during EST.

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The exercise stress test (EST) has become established as one of the most widely utilized tests in clinical cardiology.[1] Electrocardiographic variables in response to an EST such as ST segment, R-wave amplitude[2,3] or clinical indexes, i.e., anginal pain, heart rate and blood pressure responses[4–7] were used to improve the diagnostic power of the EST. Sophisticated techniques, such as multivariate analysis[8] and calculation of ST/heart rate slope[9] have also been proven to be of value for more accurate diagnosis.

Investigators have identified changes in P-wave duration and amplitude in standard leads and in V_1 in patients with valvular heart disease,[10] hypertension,[11] acute myocardial infarction[12] or chronic stable angina.[13] An increase in P-wave amplitude in normal subjects during exercise,[14] and an increase in P-wave duration was reported in patients with acute pulmonary edema which subsided on its resolution.[15] A recent study showed an increase in left atrial pressure and volume, with temporary occlusion of the left anterior descending coronary artery during angioplasty.[16] In normal subjects, during exercise, left atrial size also increased, as measured by M-mode echocardiography, but recovered rapidly after the cessation of exercise.[17] During exercise-induced myocardial ischemia indicated by chest pain, left ventricular end-diastolic and left atrial pressures increased.[18,19] This retrospective study was undertaken to determine whether P-wave changes during acute ischemic left ventricular dysfunction with EST would be of diagnostic value.

METHODS

We reviewed a grab sample of 167 angiograms and ESTs retrieved from a larger number of subjects who were studied at the Long Beach Memorial Heart Insti-

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From Memorial Heart Institute, Long Beach Memorial Medical Center, Long Beach; University of California, Irvine; and University of Southern California, Los Angeles, California. This study was supported in part by the Long Beach Memorial Medical Center Foundation, Long Beach, California. Dr. Myrianthefs was supported in part by the A.G. Leventis Foundation, Paris, France. Manuscript received May 6, 1991; revised manuscript received July 19, and accepted July 20.

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TABLE I Demographics of Control and Coronary Artery Disease Groups

	CAD	Control
Number of subjects	75	47
Men/women	55/20	31/16
Age (years)	37-79 (64)	21-73 (51)
Normal resting ECG	44	44
Previous MI	25	0
Inferior (posterior)	9	0
Anterosuperior	13	0
Posterolateral	3	0
Left ventricular hypertrophy	5	3
Right bundle branch block	1	0

CAD = coronary artery disease; ECG = electrocardiogram; MI = myocardial infarction.

tute during 1988 to 1990. Prerequisites for enrollment were: (1) the completion of a symptom-limited EST; (2) signal-averaged electrocardiogram (ECG) recorded before, during and after exercise, and the presence of sinus rhythm; (3) no evidence of chronic obstructive pulmonary disease or cardiomyopathy; (4) angiography performed within a period of 5 months with no intervening coronary events (acute myocardial infarction or unstable angina). Of this cohort, 19 subjects were excluded because of a noisy electrocardiographic recording, 14 because of previous coronary artery bypass grafting, 21 with previous angioplasty, 1 who developed ventricular tachycardia, and 1 with a thrombus in the left anterior descending coronary artery. The final study group consisted of 75 patients with coronary artery disease (CAD), and a control group of 47 normal subjects (Table I). An abnormal coronary angiogram was defined as having a stenosis of ≥50% in diameter in 1 or more of the main arteries, i.e., left anterior descending or its first diagonal branch, left circumflex artery or its obtuse marginal, right coronary artery or the posterior descending artery. Of the control group, 32 had minimal or no atherosclerosis at coronary angiography (<30% diameter stenosis in no more than 2 arteries), normal hemodynamics and normal global left ventricular wall motion in the right anterior oblique view of the contrast ventriculogram. The remaining 15 volunteers of the control group had no coronary risk factors, were free of cardiac symptoms and had normal physical findings. All subjects underwent a symptom-limited treadmill EST with the Ellestad protocol on a Marquette case 12 system. The 12-lead ECG was recorded with the Mason-Likar lead system before and during exercise, and for the first 6 minutes of recovery. We measured the maximal P duration in all leads of the signal-averaged, time-aligned ECG and the maximal P amplitude in leads V_5 and V_6, using a 5× magnifier. We identified the earliest onset and the latest offset of P waves in limb and precordial lead sets, and the longest measured P duration in either set was taken

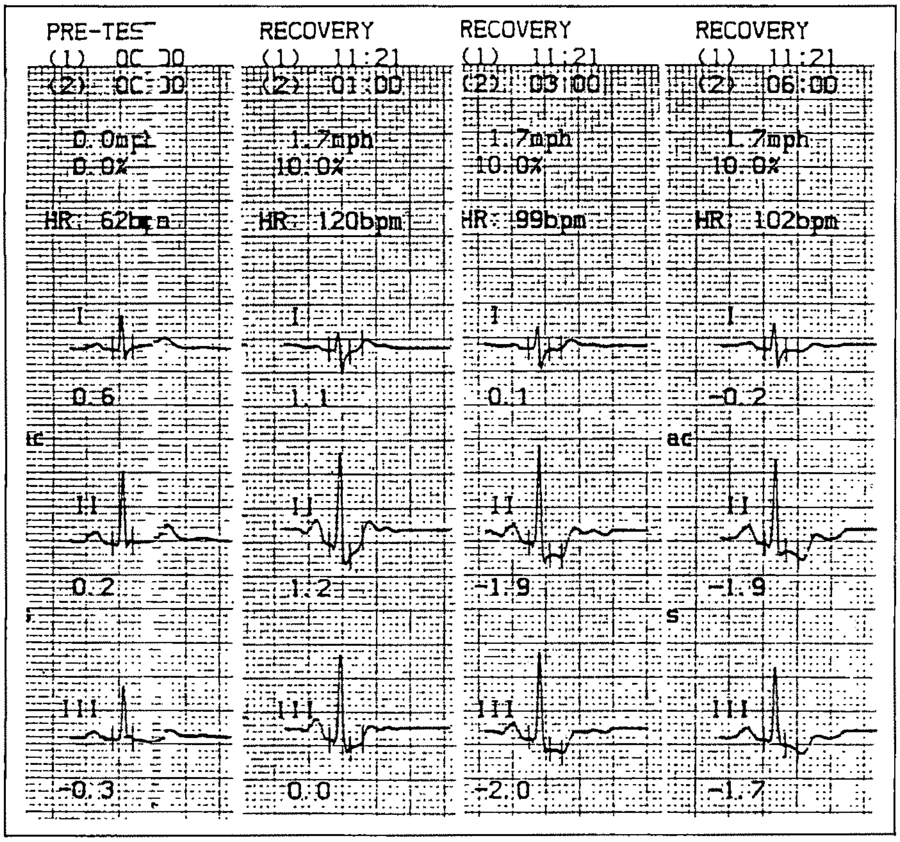

FIGURE 1. The computer-averaged, time-aligned P-QRS-T complexes of limb leads are depicted before testing and at the first, third and sixth minute in recovery (leads aVR, aVL and aVF are not shown in the figure). Total atrial activation time was measured by identifying the earliest P-wave onset and latest offset in any lead in the set. This was done also in the precordial lead set, and the longest measured P-wave duration in either set was taken as the final duration for that time period. HR = heart rate.

as the final P duration for that period (Figure 1). The PR segment was used as the isoelectric line. All durations were measured to the nearest 5 ms and amplitudes to the nearest 10 μV. All continuous variables are expressed as mean ± 1 standard deviation (SD). Statistical analysis was performed using Student's *t* test. An EST was consider abnormal when anginal pain developed during exercise or ST-segment depression or elevation ≥ 1 mm 80 ms after J point appeared; an EST was considered normal when neither of these changes were present, and equivocal when the ST segment deviated during exercise >0.5 mm and <1 mm. Sensitivity and specificity were calculated, respectively, as:

$$\text{Sensitivity} = \frac{\text{true positives}}{\text{true positives} + \text{false negatives}} \times 100,$$

$$\text{Specificity} = \frac{\text{true negatives}}{\text{true negatives} + \text{false positives}} \times 100.$$

RESULTS

The mean P amplitude before exercise in the control group was 99 ± 19 μV (± 1 SD), and was 157 ± 33, 136 ± 33, 126 ± 32, 118 ± 27, 113 ± 21, 110 ± 22 μV at the first, second, third, fourth, fifth and sixth minute of recovery, respectively. The difference in P amplitude before and after exercise was statistically significant ($p < 0.001$) at each minute of recovery. In patients with CAD, it was 98 ± 19 μV (± 1 SD), and 146 ± 36, 136 ± 35, 128 ± 31, 123 ± 30, 116 ± 28 and 113 ± 28 μV ($p < 0.001$), respectively. The differences between control and CAD groups before exercise and at each minute of recovery were not statistically significant (Figure 2). The mean P duration before exercise in the control group was 107 ± 16 ms, at the first, second, third, fourth, fifth and sixth minute of recovery it was 112 ± 17, 111 ± 16, 111 ± 14, 112 ± 13, 109 ± 13 and 109 ± 12, respectively ($p < 0.001$). In the group with CAD it was 112 ± 12 ms (± 1 SD), and 125 ± 21, 126 ± 17, 129 ± 18, 128 ± 18, 126 ± 17 and 123 ± 16 ($p < 0.001$), respectively. The differences between control and CAD groups were statistically significant throughout recovery ($p < 0.001$), and were found to be maximal at the third minute of recovery (Figure 3). Sensitivity and specificity were calculated using the conventional criteria for EST interpretation (Tables II and III). They were also calculated for an increase in P duration ≥ 5 and ≥ 20 ms from data at the second minute, alone and in combination with the above-mentioned standard criteria. This time was chosen because individual changes in P duration yielded the most significant results. By using P duration delta ≥ 20 ms as an additional parameter to the conventional criteria, the sensitivity increased from 57 to 75%, with a

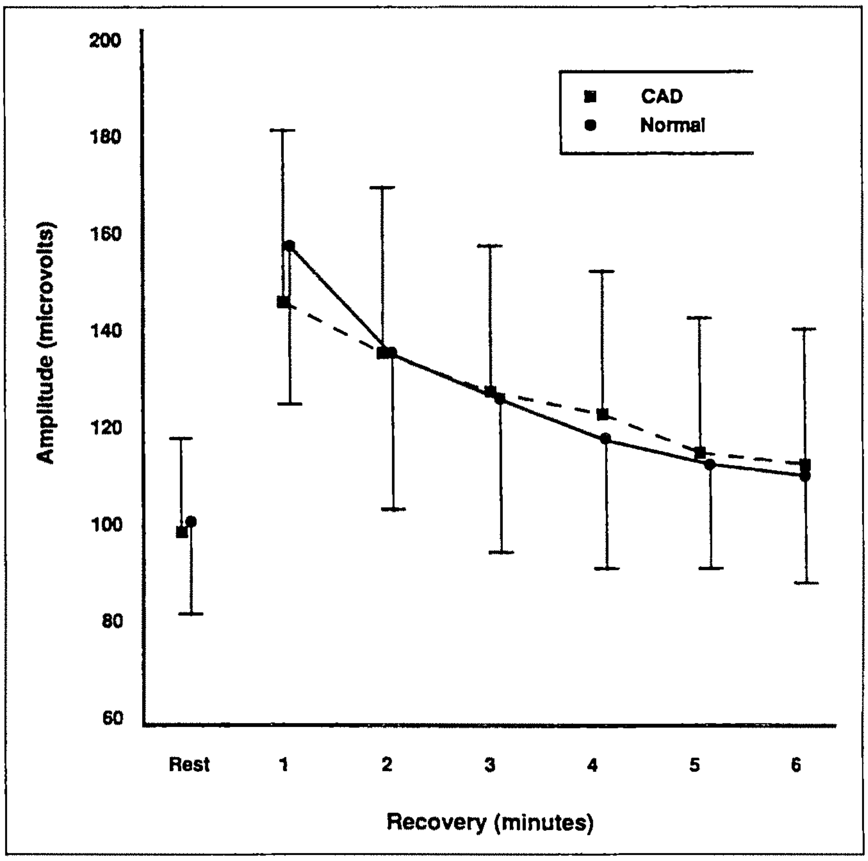

FIGURE 2. P-wave amplitude plotted during recovery in control and coronary artery disease (CAD) groups. *Brackets* indicate ± 1 standard deviation. Differences between rest and all 6 minutes after exercise were significant ($p < 0.001$) for both groups. Differences between control and CAD groups were not significant at rest or at any minute in recovery.

concomitant small decrease in specificity of 85 to 77%. We also applied the same criteria in the subgroup with 3-vessel disease (Table III).

DISCUSSION

The improvement of the diagnostic power of the EST has been an attractive goal for many years. In the past, using ST criteria, sensitivities of 50 to 78%, and specificities of 80 to 90% have been reported.[20,21] It has been shown that sensitivity can be increased by applying <1 mm of ST depression, but always at the expense of specificity.[22] Specificity can also be increased by requiring depression of >1 mm, but at the expense of sensitivity.

The latter portion of the P wave represents the left atrial depolarization. As the left atrium enlarges, the duration of the terminal, posterior and leftward compo-

TABLE II Calculation of Sensitivity and Specificity by Applying Various Diagnostic Criteria in Coronary Artery Disease and Control Groups at the Second Minute in Recovery

Diagnostic Criteria	Exercise Stress Test Result: Control Nor.	Abn.	Eq.	CAD Nor.	Abn.	Eq.	Sen.* (%)	Spec.* (%)
ST ↓ ≥1 mm or ST ↑ ≥1 mm or anginal pain	34	7	6	13	43	19	57	85
Pdur delta ≥5 ms	24	23	0	23	52	0	69	51
ST ↓ ≥1mm or ST ↑ ≥1 mm or anginal pain or Pdur delta ≥5 ms	23	23	1	6	65	4	87	51
Pdur delta ≥20 ms	30	17	0	14	61	0	81	64
ST ↓ ≥1 mm or ST ↑ ≥1mm or anginal pain or Pdur delta ≥20 ms	32	11	4	10	56	9	75	77

*For sensitivity and specificity calculations, equivocal tests were included as negative.
Abn. = abnormal; CAD = coronary artery disease group; Eq. = equivocal; Nor. = normal; Pdur delta = increase in P-wave duration from rest; Sen. = sensitivity; Spec. = specificity; ↓ = depression; ↑ = elevation.

TABLE III Calculation of Sensitivity and Specificity by Applying Various Diagnostic Criteria in the Subgroup with Three-Vessel Disease (n = 20)

Diagnostic Criteria	Exercise Stress Test Result: Nor.	Abn.	Sen. (%)	Spec. (%)
ST ↓ ≥1 mm or ST ↑ ≥1 mm or anginal pain	4	16	80	85
Pdur delta ≥5 ms	4	16	80	51
ST ↓ ≥1 mm or ST ↑ ≥1 mm or anginal pain or Pdur delta ≥5 ms	0	20	100	51
Pdur delta ≥20 ms	10	10	50	64
ST ↓ ≥1 mm or ST ↑ ≥1 mm or anginal pain or Pdur delta ≥20 ms	2	18	90	77

Abbreviations as in Table II.

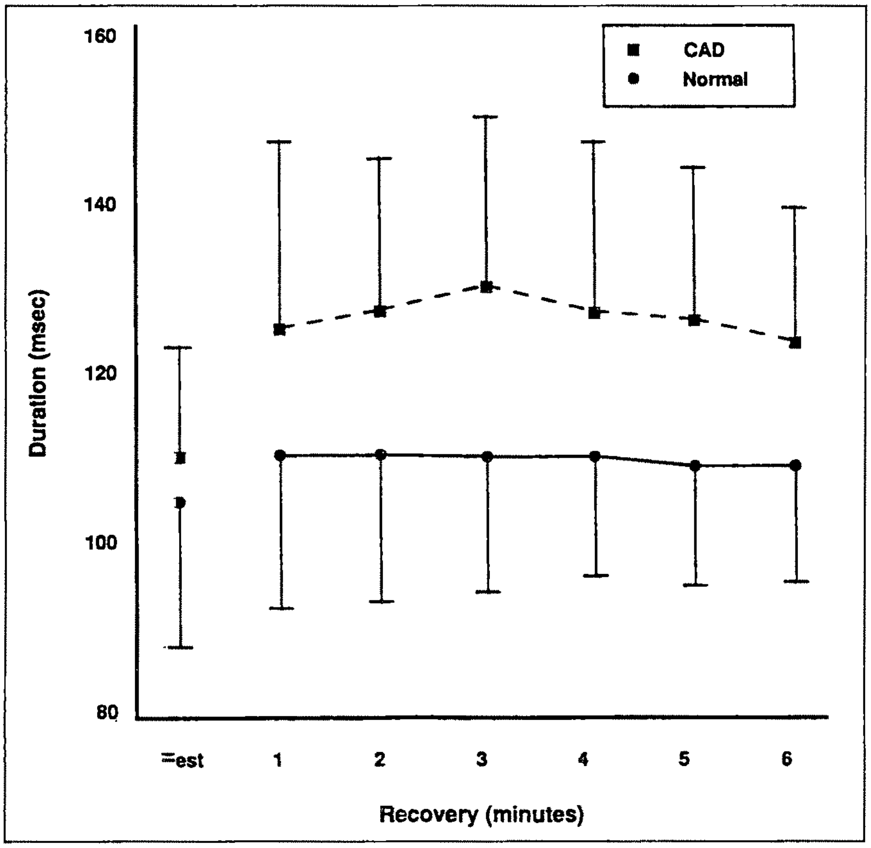

FIGURE 3. P-wave duration plotted during recovery in control and coronary artery disease (CAD) groups. *Brackets* indicate ± 1 standard deviation. Differences between the 2 groups are not statistically significant during rest but are statistically significant during all 6 minutes after exercise (p <0.001).

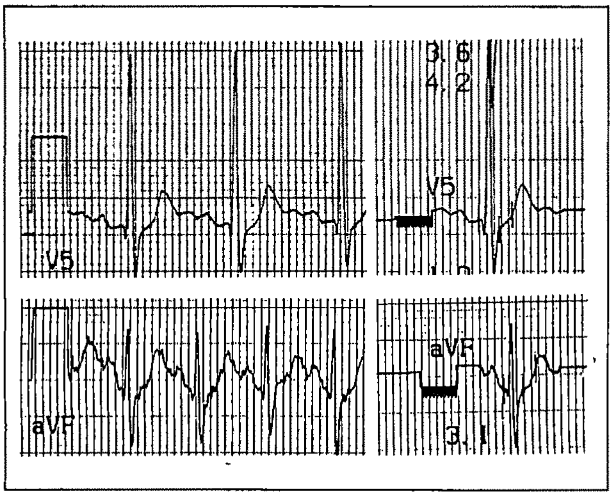

FIGURE 4. Examples of U- and P-wave overlap *(upper panel)*, and T- and P-wave overlap *(bottom panel)* from different subjects are seen, as well as the corresponding signal-averaged beats *(right column)* in recovery.

nent of the P wave is increased, resulting in P-wave prolongation.[23,24]

Our hypothesis is that exercise-induced left ventricular ischemia impacts the left atrial component of the P wave due to transient left ventricular diastolic dysfunction, increased left ventricular filling pressure, and increased mean left atrial pressure and volume, which lengthens total left atrial activation time. Yokota Y et al[25] reported an increase in P-wave duration after exercise in patients with mitral stenosis, hypertension or old myocardial infarction, whereas Yokota M et al[26] studied the exercise-induced orthogonal P-wave changes and found a statistically significant increase in the maximal horizontal P-vector magnitude 30 seconds after exercise in patients with CAD when compared with normal subjects. In the present study P-wave duration was found significantly prolonged even at the sixth minute in recovery. This finding is explained by the observation that left ventricular diastolic function is impaired early in ischemia and is slow to recover.[27]

Study limitations: The problems encountered in measuring P-wave duration during early recovery were: T- and P-wave overlap that happened in most control subjects and patients, resulting in foreshortening of the P wave to a similar proportion in both groups; U- and P-wave overlap was also a frequent occurrence during early recovery, having the same result (Figure 4, Table IV). Froning and Froelicher[28] reported a detailed analysis of this problem. The P-wave onset was occasionally obscured by the computer algorithm at higher heart rates in subjects with longer PR intervals. This was due to a shorter recording window before the QRS that represents ¼ of the RR interval. Because of the longer window after QRS representing ¾ of RR interval, the first ¼ of the next cycle including the next P onset was reproduced. The signal-averaged ECG provides improved signal to noise ratio, but the manual measurement of the P wave is quite tedious, time consuming and requires considerable magnification. It is likely that computer identification of P-wave onset and offset in the multilead spatial vector magnitude would be more reliable and would enhance the practical application of this method.

TABLE IV Varieties of Potential Interference with P-Wave Measurements at Different Times During Recovery

Overlap	CAD (n = 57)	Control (n = 36)
T-P (1st min)	23 (40%)	27 (75%)
T-P (2nd min)	11 (19%)	11 (30%)
T-P (3rd min)	8 (14%)	9 (25%)
T-P (4th min)	0 (0%)	1 (2%)
U-P (1st min)	4 (7%)	3 (8%)
U-P (2nd min)	0 (0%)	5 (13%)
U-P (3rd min)	0 (0%)	2 (5%)

CAD = coronary artery disease group; P = P wave; T = T wave; U = U wave.

We believe that measuring P-wave duration provides information related to exercised-induced ischemic left ventricular diastolic dysfunction. Increase in P-wave duration found in recovery combined with the standard variables for EST interpretation, holds promise of increasing diagnostic power. If confirmed by more extensive experience, P-wave duration may add to our ability to identify ischemia with exercise.

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Assessment of Medial Thinning in Atherosclerosis by Intravascular Ultrasound

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This study investigated the in vitro (40 MHz) and in vivo (30 MHz) feasibility of intravascular ultrasound to document the influence of atherosclerotic lesions on the typical 3-layered appearance of muscular arteries.

The in vitro images of 39 arteries were compared with the corresponding histologic sections. Media and lesion thickness were measured at the areas of minimal and maximal lesion thickness. The median media thickness was 0.8 mm in the absence of a lesion, decreasing to 0.3 mm in the area of maximal atherosclerosis. The ultrasonic data correlated closely with histologic measurements (0.6 and 0.3 mm, respectively).

The in vivo study was performed in 29 patients undergoing coronary or peripheral vascular procedures. A total of 150 still-frames were selected for quantitative analysis. The median media thickness was 0.6 mm in the absence of a lesion, decreasing to 0.1 mm in the area with maximal atherosclerosis. This study revealed that intravascular ultrasound imaging accurately determines that media thickness of muscular arteries is inversely related to lesion thickness. In vitro data, verified with histology, can be translated to humans in vivo.

(Am J Cardiol 1991;68:1625–1632)

A new imaging method, catheter-based intravascular ultrasound, has had the capacity to provide qualitative[1–5] as well as quantitative[6–12] assessment of arterial morphology and dimensions. With intravascular ultrasound, encouraging data have been obtained in vitro to differentiate elastic from muscular arteries, and to distinguish between the various components of atherosclerotic lesions.[7,8,13,14]

Intravascular ultrasonic in vitro studies have indicated that lesion location and thickness can accurately be determined in the presence of a visible landmark determined by a hypoechoic media in a muscular artery.[7,14] An atherosclerotic lesion may obscure this medial reference band due to ultrasound attenuation, especially in advanced stages when fibrosis and calcium are present. Furthermore, histologic studies have shown that atherosclerosis affects the media and, in advanced stages, may obliterate the media entirely.[15–18]

The aim of this study was to evaluate the potential of intravascular ultrasound to provide quantitative data in vitro for assessing the effect of atherosclerosis on the arterial media of muscular arteries, to compare these data with those from corresponding histologic sections, and with in vivo data from normal and diseased human peripheral arteries.

METHODS

Intravascular ultrasound: In a laboratory set-up, a 1 mm diameter, 40 MHz, mechanically rotated, single-element transducer mounted on an 8Fr catheter was used for in vitro studies. For in vivo study, a 5Fr mechanically motor-driven, rotating imaging catheter was used with a 1 mm diameter, 30 MHz transducer. The axial resolution of the 40 and 30 MHz systems was 75 and 80 μm, respectively; the lateral resolution was better than 200 and 225 μm, respectively, at a depth of 1 mm (Du-Med, Rotterdam, the Netherlands). The images were displayed on a monitor by means of a video-scanned memory of 512 × 512 pixels with 256 shades of gray. Markers were displayed for calibration purposes. For review and analysis the ultrasound images were recorded on VHS videotape together with calibration markers.

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Human specimens: Intravascular ultrasound was evaluated in [illegible] human vascular specimens of muscular nature obtained 2 to 14 hours after death. They include coronary, iliac, femoral, popliteal, mesenteric and renal artery. The details of processing the specimens, echographic imaging and histologic preparation have been described previously.[5,7] For each vascular specimen studied, 1 histologic cross-section with the most significant lesion thickness was selected and compared with the corresponding ultrasonic cross-section. Photographs were obtained of the ultrasonic images and histologic sections (the latter together with a 1 mm calibrator).

Patient studies: Seven patients undergoing diagnostic cardiac catheterization and 22 patients undergoing balloon angioplasty of the superficial femoral artery were studied after signing an informed consent. An introducer sheath was placed into the femoral artery for diagnostic catheterization and intervention. In 3 patients in whom the superficial femoral artery was totally occluded, laser therapy was performed (Nd-YAG, Medilas – 2, Messerschmidt Bölken Blöhm) to create a lumen accessible for the intravascular ultrasound study. The intravascular ultrasound catheter was advanced through the sheath in a retrograde manner into

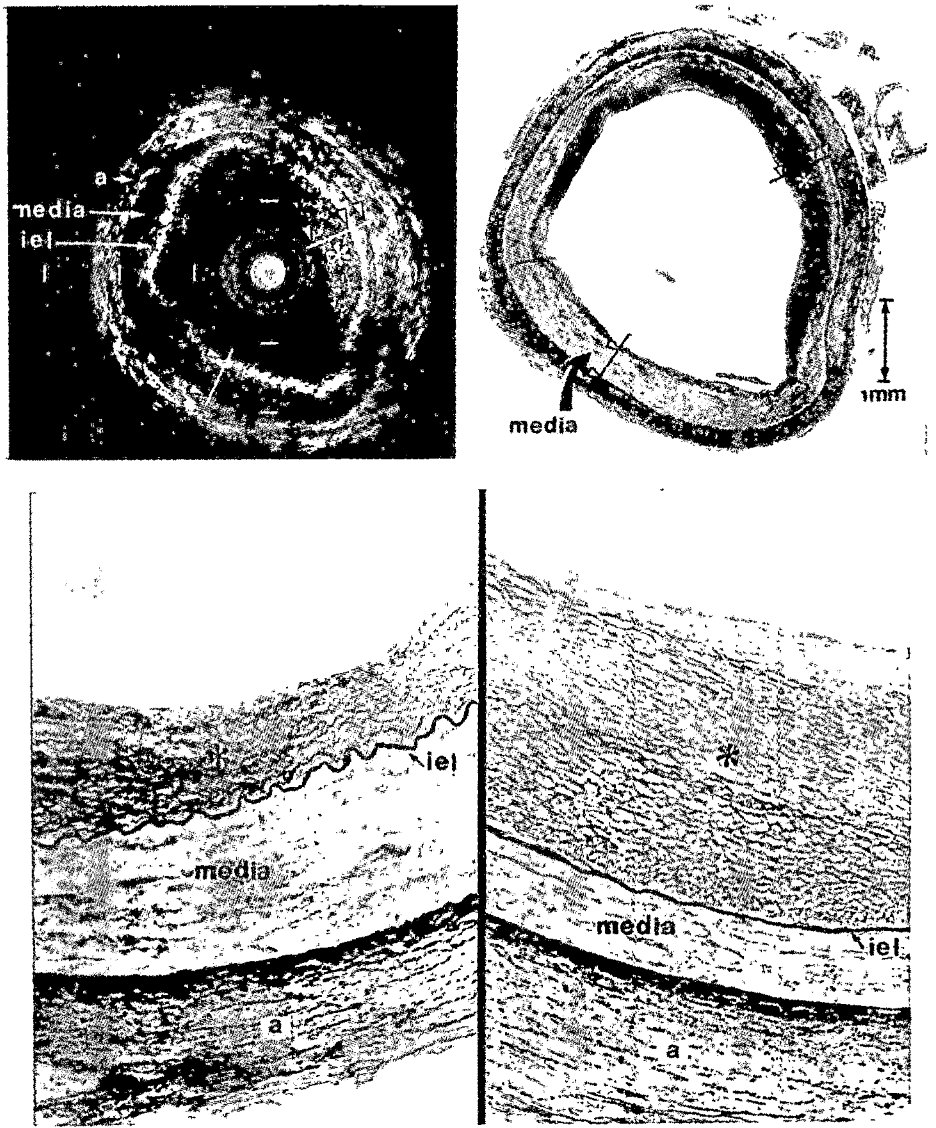

FIGURE 1. Ultrasonic cross-section obtained in vitro (40 MHz) from a renal artery together with photomicrographs of the corresponding histologic cross-section. The media of this muscular artery, mainly composed of smooth muscle cells, appears characteristically hypoechoic on ultrasound. Bright echoes of the internal elastic lamina (iel) and adventitia (a) circumscribe the hypoechoic media. The lesion is noted echographically at 7 o'clock. Diffuse intimal thickening, most prominent at 2 o'clock *(asterisk)*, is lying in a shallow pouch of the media. Media thickness is influenced by the presence of the lesion *(arrow heads)*. *Lower panel* details the changes caused by the lesion to the histologic architecture of the arterial media *(asterisk)*. An insignificant lesion corresponded with a corrugated internal elastic lamina *(left panel)*; a significant lesion was associated with a stretched internal elastic lamina *(right panel)*. Echographically, both structures were equally bright (compare 7 and 2 o'clock). (Verhoeff van Gieson stain [calibration 1 mm], magnification: *top,* ×16; *bottom,* ×90.)

the iliac artery (n = 7) and in an anterograde manner into the femoral artery (n = 22). Continuous recordings were obtained at different sites of the arterial system before diagnostic catheterization and intervention. A total of 150 representative still-frames were selected and photographed for quantitative analysis.

Quantitative analysis: From the in vitro cross-sectional ultrasonic images the media and lesion thicknesses were measured independently by 2 observers at 2 sites: where lesion thickness was minimal and maximal (Figures 1 to 4). Linear regression analysis was applied to establish the correlation between ultrasonic and histologic measurements on both maximal lesion and media thicknesses (Figure 5). Wilcoxon's signed rank test was used to determine interobserver compatibility.

For the in-vitro study, histologic measurements were obtained independently from the echographic cross-sections and were used as the reference standard. A lesion was defined as present when seen superimposed on the hypoechoic media ($\geq$0.1 mm). Lesion thickness was calculated as the perpendicular distance between the lesion surface, i.e., intimal leading edge and the leading edge of the internal elastic lamina. The corresponding media thickness was calculated as the distance between the leading edge of the internal elastic lamina and the leading edge of the adventitia (Figure 1). In the absence of a distinct internal elastic lamina the junction lesion versus hypoechoic media was used (Figure 2). In the presence of calcification, the media could not be envisioned because of ultrasonic shadowing. These regions were excluded for comparison. Instead the area showing a measurable maximal lesion thickness was chosen (Figure 2). In the ultrasound images where lesion could not be acoustically separated from the un-

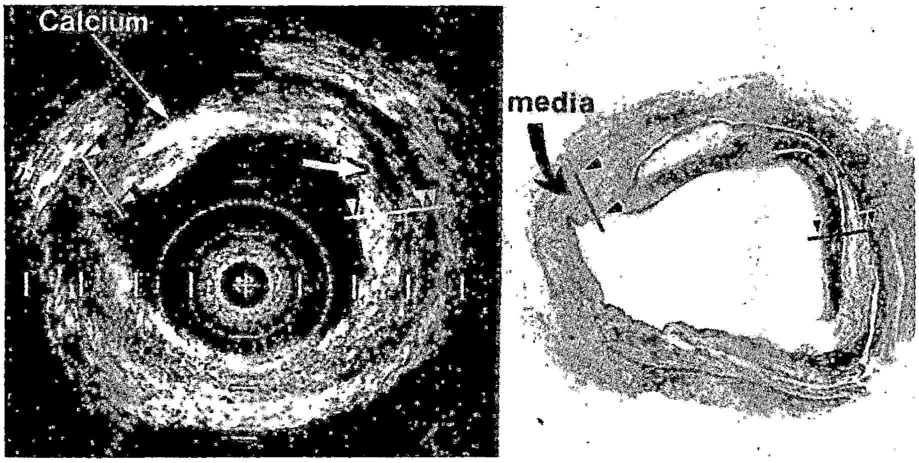

FIGURE 2. Ultrasonic cross-section obtained in vitro (40 MHz) with corresponding histologic cross-section of a femoral artery showing a classic eccentric atherosclerotic lesion. The lesion-free wall showing a distinct media is seen between 5 and 10 o'clock. Media thickness was measured at 10 o'clock. Distinct medial thinning in the presence of an atherosclerotic lesion is seen at 3 o'clock. Note that calcium seen at 11 o'clock is casting ultrasonic shadowing. The hypoechoic region inside the lesion at 2 o'clock *(arrow)* corresponds with lipid. Calibration 1 mm. (Verhoeff van Gieson stain, magnification ×7.)

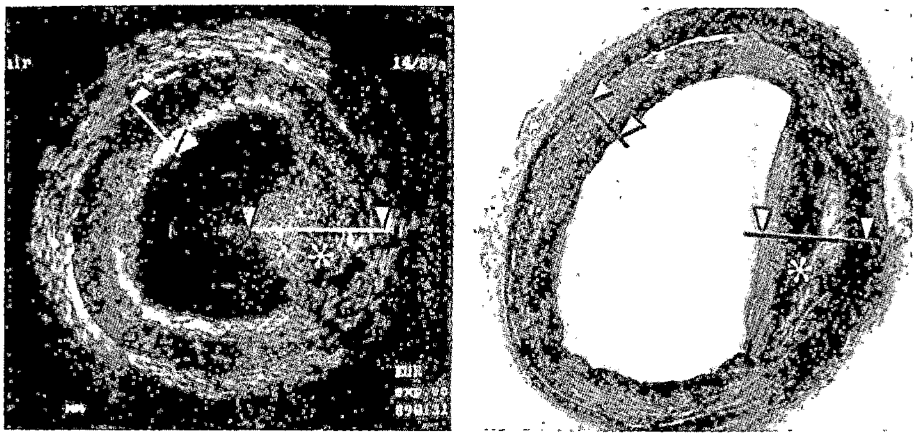

FIGURE 3. Ultrasonic cross-section obtained in vitro (40 MHz) together with the corresponding photomicrograph of the histologic cross-section obtained from a mesenteric superior artery. Bright echoes of internal elastic lamina and adventitia circumscribe the hypoechoic media. A distinct media was observed echographically in the absence of a lesion (at 10 o'clock). In the presence of an extensive lesion *(asterisk)* the media becomes invisible echographically. The corresponding histology reveals absence of the media in this region. (Verhoeff van Gieson stain [calibration 1 mm], magnification ×6.)

derlying media, the media thickness was classified as absent (Figures 3 and 4). In the presence of a fibrous lesion with sufficient collagen casting a shadow, the maximal measurable lesion was calculated with ultrasound, and the corresponding invisible media was classified as absent. Similar to the in vitro quantification study, media and lesion thicknesses in vivo were measured at the sites where lesion thickness was minimal and maximal (Figures 6 to 8).

To establish the correlation between the media and lesion thicknesses, the difference in media thickness measured at the sites of minimal and maximal lesion thickness were evaluated by means of the sign test.[19]

RESULTS

In vitro studies: Ultrasound and histologic examination in vitro revealed no lesion in 3 cross-sections, a concentric lesion in 3 other specimens and an eccentric lesion in 33 specimens. Evidence of calcium noted echographically in 11 cross-sections was confirmed histologically.

Linear regression analysis between intravascular ultrasound and histologic measurements for maximal lesion and media thicknesses showed each a correlation coefficient of $r = 0.83$ ($p < 0.00001$ in both cases) (Figure 5).

There was good agreement between the 2 observers, with no significant difference in measurements of media and lesion thickness ($p > 0.10$ in all cases). The correlation coefficients between the measurements of the 2 observers varied from $r = 0.73$ to $r = 0.97$.

With use of the sign test, correlation was significantly negative ($p < 0.00001$ in all cases) for both observers and for echographic and histologic measurements (Fig-

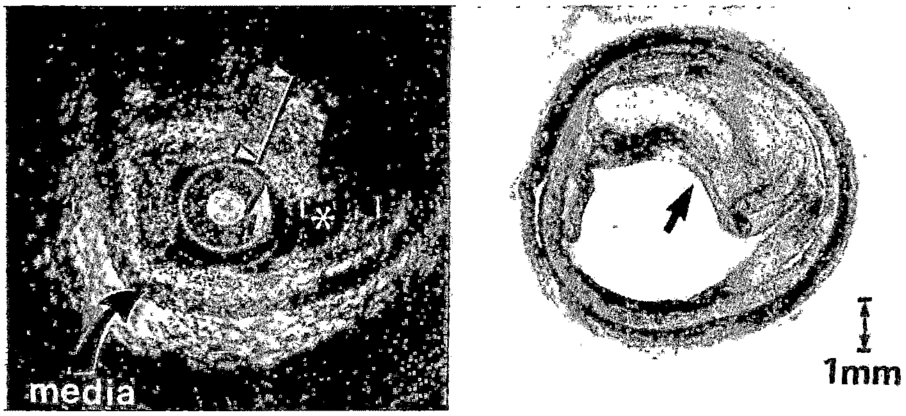

FIGURE 4. Intravascular ultrasound cross-section obtained in vitro (40 MHz) from a femoral artery with the corresponding histologic cross-section. The lesion-free arterial wall showing a distinct media is seen between 4 and 9 o'clock. On the opposite side a large atherosclerotic lesion is present *(arrow)*. Clear imaging of the remote tissues was not possible with ultrasound, probably due to the collagen present in this lesion. The hypoechoic region at 3 o'clock *(asterisk)* is due to a dissection. *Arrowheads* indicate the maximal lesion thickness measured echographically. (Verhoeff van Gieson stain [calibration 1 mm], magnification ×6.)

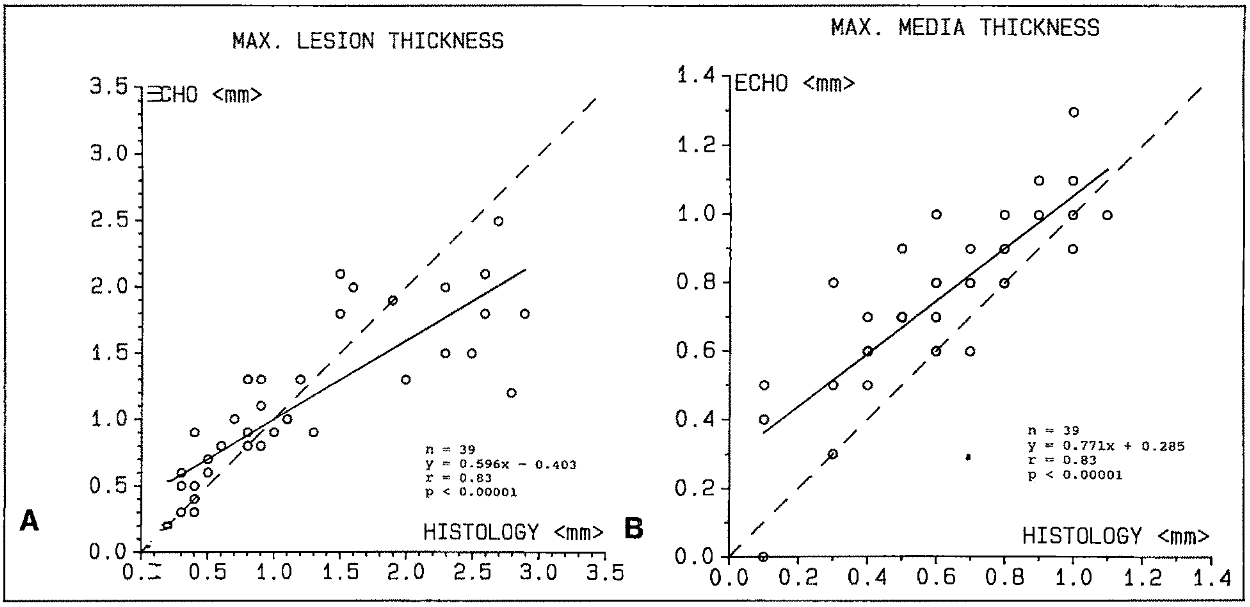

FIGURE 5. Linear regression analysis between intravascular ultrasound and histology for maximal (MAX.) lesion thickness *(A)* and maximal media thickness *(B)* in millimeters.

ure 9). Because distribution of the data was rather skewed, the location of a distribution was characterized by the median and the variability by the interquartile range. Table I lists the parameters, median, range and interquartile range. A decrease in median media thickness (0.8 to 0.3 mm) is inversely proportional to an increase in median lesion thickness (0.0 to 1.0 mm) measured at the same location. Measurements from the histologic cross-sections were concordant (Table I, Figure 9).

In the ultrasound images where lesion could not be acoustically separated from the underlying media (n = 10), corresponding histology revealed a fibrotic lesion and a media thickness of 0.0 mm in 4, 0.1 mm in 3 and 0.2 mm in 3 specimens, respectively.

In vivo studies: In all patients, intravascular ultrasound studies provided high resolution real-time, cross-sectional images. There were no complications caused by the ultrasound study. The presence of a hypoechoic layer, giving a characteristic 3-layered appearance of both iliac and superficial femoral arteries, was defined in all instances. From the in vitro information, we conclude that the hypoechoic vascular layer corresponds with the media of a muscular artery. In the iliac artery, normal vascular morphology without evidence of a superimposed lesion was found. In the superficial femoral artery normal segments as well as cross-sections with nonobstructive and obstructive lesions were envisioned (Figures 6 to 8). In 21 still-frames, ultrasound shadowing was noted beyond the area of a lesion that may have contained calcium.

Quantitative measurements in vivo (derived from 150 still-frames) showed that in the absence of a lesion, median value of media thickness was 0.6 mm. In the presence of an atherosclerotic lesion, the media was reduced in thickness to a median value of 0.1 mm (Table I).

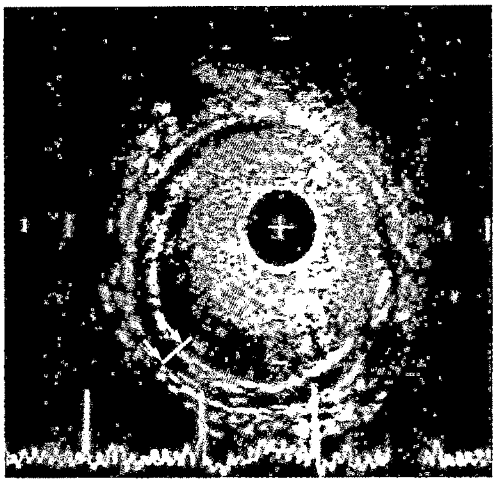

FIGURE 6. Ultrasonic cross-section obtained in vivo (30 MHz) representing a normal femoral artery. The 3-layered appearance of the arterial wall is similar to that seen in the in vitro study (compare Figures 1 and 4). Media thickness is indicated by *arrows*. Echogenicity of blood is seen within the arterial lumen (calibration 1 mm).

DISCUSSION

The results of this study support the hypothesis that intravascular ultrasound is able to evaluate the manner in which the media of a muscular type of artery is affected by atherosclerosis. The hypoechoic media was always typically seen adjacent to the bright adventitia, whereas hypoechoic zones due to lipid deposits or dissection were typically present inside or near a lesion (Figures 2 and 4).

Definite medial thinning was noted in vitro in undistended vessels and in vivo in vessels under pressure. Media thickness measured echographically and histologically decreased 60 and 50%, respectively, in diseased segments compared with disease-free wall segments of the same vessel. Although a few observations in this study showed discordant measurements, the

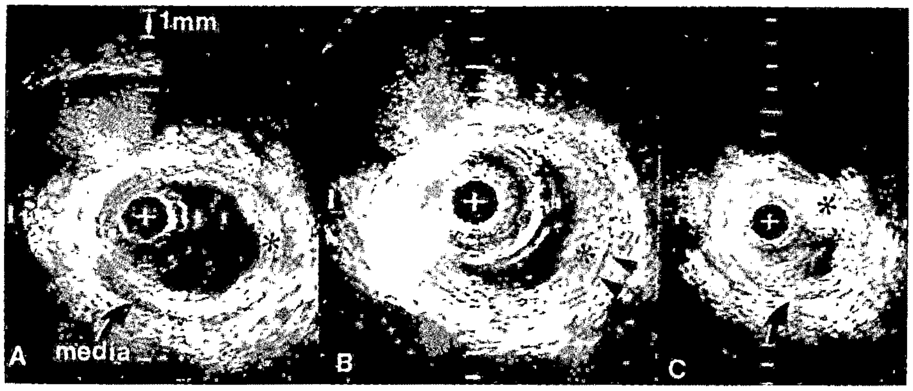

FIGURE 7. Ultrasonic cross-sections obtained in vivo (30 MHz) in a patient undergoing balloon angioplasty of the superficial femoral artery. The cross-sections *(A to C)* are taken from 3 different levels in the femoral artery and are arranged proximal to distal. *A*, proximally the lumen is not obstructed. There is evidence of diffuse intimal thickening *(asterisk)*. The dark layer corresponds with the hypoechoic media *(bold arrow)*. *B*, more distally the lesion *(asterisk)* is seen to expand progressively, resulting in conspicuous medial thinning at 3 o'clock *(arrowheads)*. *C*, finally the ultrasound catheter images the atherosclerotic lesion *(asterisk)* casting a shadow at 1 o'clock. Between 1 and 4 o'clock the lesion prevents visualization of the media. Media is visible between 5 and 1 o'clock *(bold arrow)*. At 11 o'clock a vein is noted (calibration 1 mm).

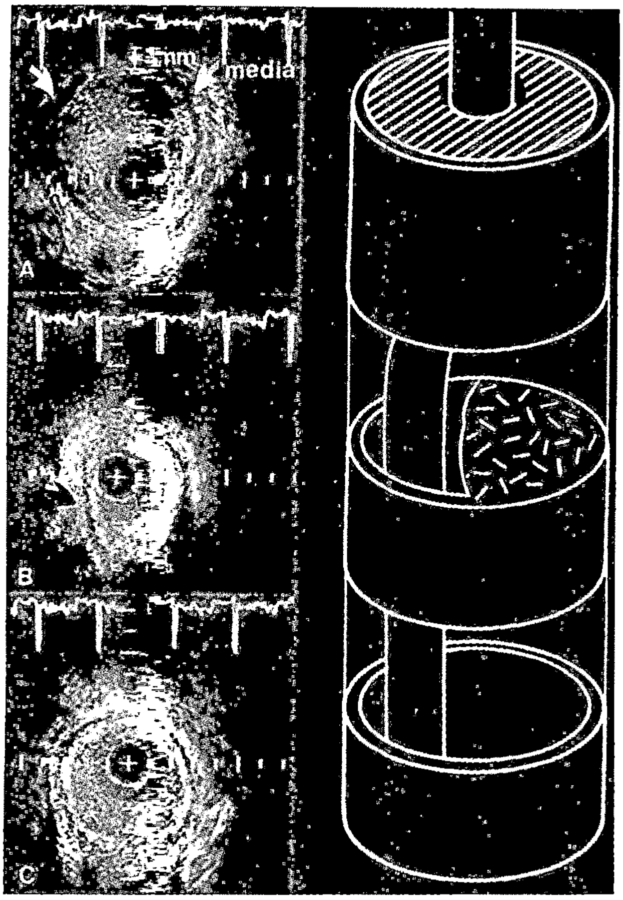

FIGURE 8. Ultrasonic cross-sections and corresponding diagram obtained in vivo (30 MHz) from a patient with obstructive disease of the superficial femoral artery. *A*, proximally the lumen is seen completely filled with a lesion. Real-time images revealed no normal movement of blood in this cross-section. The dark layer *(bold arrow)* corresponds with the media. *B*, at the level of stenosis the medial layer *(bold arrow)* is visible only between 7 and 11 o'clock, indicating an eccentric lesion. *C*, more distally a normal vessel geometry with a hypoechoic media is identified in which blood flow was recognized (calibration 1 mm).

overall evaluation revealed an inverse relation between the lesion and media thickness (Figure 9).

The frequency of the 2 echographic systems used for the in vitro (40 MHz) and in vivo (30 MHz) studies differed by one-third octave; their axial resolution was comparable. Comparison of mean data of media thickness measured with ultrasound in vitro (0.8 mm) and in vivo (0.6 mm) at the site of a minimal lesion showed a difference of 0.2 mm (25%) (Table I). We believe that this difference is due to the influence of blood pressure. The observation is further validated by recent in vitro work at our laboratory indicating that pressure reduced arterial wall thickness to one-third of its unpressurized state (unpublished observations). Furthermore, no significant difference was found in media thickness when calculated from diastolic and systolic still frames, suggesting that blood pressure had no notable influence on media thickness during the cardiac cycle itself.

Our data on decrease in media thickness correlated closely with that of other histologic studies (60 and 55%, respectively) on diseased coronary arteries.[16–18] This supports the contention that medial thinning is an essential part of atherosclerosis.[16] The lesion, seen lying in a shallow pouch of the media, may lead to medial thinning and, consequently, to an increase in internal elastic lamina area. Thus, the artery may enlarge as a result of a developing lesion on the underlying wall.[20] Intravascular ultrasound imaging has the unique potential to document the positive relation between arterial size and the degree of atherosclerosis.[21]

Furthermore, we observed that media thickness is inversely related to the extent of atherosclerosis. In vitro data revealed that minor lesions, histologically classified as diffuse intimal thickening,[22,23] were associated with

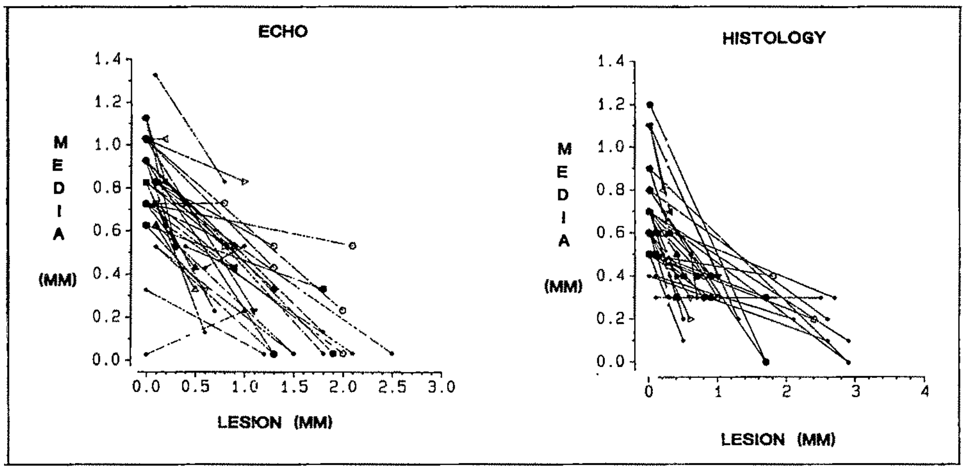

FIGURE 9. Sign test: graphs showing ultrasonic and histologic measurements of matched lesion and media thickness measured in millimeters at the minimal and maximal lesion sites, interconnected. Each segment is represented by a specific symbol to connect the media thickness at the sites of minimal and maximal lesion thickness. Corresponding symbols in echo and histology represent the same segment.

TABLE I Media and Lesion Thickness (median value, interquartile range and range) Determined In Vitro (n = 39) and In Vivo (n = 150) Using Intravascular Ultrasound in the Area with Minimal and Maximal Lesion Thickness

	In Vitro Echo			Histology			In Vivo Echo		
	M	IR	R	M	IR	R	M	IR	R
Minimal lesion	0.0	(0.0–0.1)	(0.0–0.6)	0.0	(0.0–0.1)	(0.0–0.4)	0.0	(0.0–0.0)	(0.0–1.5)
Media	0.8	(0.6–0.9)	(0.0–1.3)	0.6	(0.4–0.8)	(0.1–1.1)	0.6	(0.4–0.7)	(0.1–0.9)
Maximal lesion	1.0	(0.6–1.5)	(0.1–2.5)	0.9	(0.4–1.9)	(0.2–2.9)	1.5	(1.0–2.0)	(1.0–2.0)
Media	0.3	(0.0–0.5)	(0.0–1.0)	0.3	(0.1–0.4)	(0.1–0.8)	0.1	(0.0–0.4)	(0.0–0.9)

All parameters are expressed in millimeters.
IR = interquartile range; M = median value; R = range.

some degree of medial thinning. Histologically classified atherosclerotic lesions were associated with significant medial thinning. Because of calcium in the atherosclerotic lesion, the maximal region of the lesion could not be identified echographically. This occurred echographically in 11 cross-sections and corresponding histology confirmed the presence of calcium. However, the presence of calcium itself is an indication that the lesion represents a more advanced stage of the disease.[22,23] This is of major clinical importance for in vivo interpretation using intravascular ultrasound. A distinct 3-layered appearance was observed in vivo in the iliac and femoral artery. Distinct medial thinning was seen in the presence of atherosclerosis. Similarly, ultrasound shadowing was noted in vivo (in 21 cross-sections) beyond the area of a lesion that may have contained calcium. Conversely, despite a large lesion filling the entire lumen area of a femoral artery in 6 patients, medial thinning had not occurred. The lesion was located proximal to the atherosclerotic lesion in the same vessel (Figure 8). We assumed that the structure presented a young rather than an old atherosclerotic lesion, since visualization of the medial layer was not hampered. This assumption is further validated by the fact that histologic study by atherectomy in 2 of these patients revealed thrombus. Thus, the underlying media thickness may be a helpful guide during in vivo studies to determine the nature of the lesion.

Limitations of intravascular ultrasound: With regard to the frequency used for the in vitro studies (40 MHz), the medial layer may be better visualized in the presence of a large fibrous lesion with a transducer of lower frequency. In this study, the media was echographically deemed absent in 6 cross-sections, whereas histologic examination revealed a media thickness of 0.1 and 0.2 mm, respectively.

The noncoaxial positioning as well as the eccentric location of the catheter may influence the precision of the medial measurement. In the in vitro studies, care was taken to avoid eccentricity and misalignment of the catheter. To overcome this problem in the in vivo setting, a large number of still-frames were evaluated.

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Coronary Hemodynamics and Coronary Flow Reserve After Intracoronary Diltiazem in Humans

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To analyze the effect of the calcium antagonist diltiazem on coronary hemodynamics, epicardial coronary artery diameter, coronary blood flow and coronary blood flow velocity were assessed at baseline and after a 0.5 mg intracoronary bolus of diltiazem in nonstenotic coronary arteries of awake humans. Patients (n = 20) were first randomized to pretreatment with either placebo (n = 10) or isosorbide dinitrate (0.5 μg/kg/min infusion; n = 10), and coronary flow reserve was measured before and after administration of diltiazem. There were significant increases in epicardial coronary artery diameter (10%; p = 0.0001) and coronary blood flow (30%; p = 0.0001) in all patients after administration of diltiazem. Whereas basal coronary blood flow velocity increased only slightly (7%; p = not significant), there was a significant decrease in coronary flow reserve (10%; p = 0.004). Increases in coronary diameter and blood flow after diltiazem were comparable in patients pretreated with placebo or nitrates. However, the decrease in coronary flow reserve was significant only in patients pretreated with placebo (19%; p = 0.0008). This reduction in coronary flow reserve could be due to "raising the floor" (increased baseline coronary blood flow) or "lowering the ceiling" (reduction of maximal coronary blood flow).

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Calcium antagonists are known to dilate coronary epicardial vessels, and previous work has also indicated a possible effect of some of these drugs on the coronary resistance vessels.[1] Experimental studies have suggested that calcium antagonists cause partial blunting of the coronary hyperemic reaction after brief coronary occlusions.[2-3] Coronary flow reserve is a useful index of the vasodilator capacity of coronary circulation. Its measurement has been used primarily to assess the physiologic significance of coronary stenoses.[4] The reduction of the maximal distal vasodilator capacity by calcium antagonists may represent another mechanism of action of these drugs.[5]

Recently, Rossen et al[6] studied the effect of intravenous and intracoronary diltiazem on coronary flow reserve in awake humans pretreated with nitrates. Because no effect on this parameter was observed, they concluded that attenuation of maximal coronary dilation did not explain the known antianginal effect of diltiazem. Because in their study nitrates could have masked the effects of diltiazem, we studied the coronary flow reserve response to intracoronary diltiazem (0.5 mg) in 20 patients randomly assigned to receive pretreatment with either placebo or nitrates.

METHODS

Patient selection: Patients ≤70 years of age were eligible for this study if they were candidates for 1-vessel angioplasty of a ≥70 but <100% diameter stenosis of a major coronary artery, and if the diagnostic coronary angiogram showed a nonstenotic left anterior descending or circumflex artery from which the atrioventricular nodal artery did not originate. Antianginal medication was withheld ≥24 hours before study entry, except for sublingual nitrates, which were allowed until 6 hours before the procedure. Left ventricular ejection fraction at rest was always ≥50%. Patients with arterial hypertension (blood pressure >180/100 mm Hg) or hypotension (systolic pressure <100 mm Hg) at study entry were excluded. A heart rate <50 beats/min, and presence of any degree of atrioventricular block and of any other cardiovascular disease were also exclusion criteria. Patients were also excluded if angioplasty procedure was unsuccessful or if, during angioplasty, the administration of other vasoactive medication was indicated. The research protocol was approved by the Uni-

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versity of Leuven Ethical Committee, and informed consent was obtained from each subject before the beginning of the procedure.

Study design (Figure 1): Patients were randomly assigned to pretreatment with placebo or nitrates before angioplasty. In the group pretreated with nitrates, isosorbide dinitrate was administered intravenously (0.5 μg/kg/min). The group pretreated with placebo received sodium chloride (0.9%) intravenously at the same flow rate. Before angioplasty, all patients received a bolus of 10,000 IU heparin intravenously followed by a continuous infusion of 1,000 IU/hr. No other premedication was used. The procedure was performed as described previously.[7] The study was begun in the nonstenotic contralateral coronary artery only if the angioplasty procedure was successful (residual stenosis <50%). The diameter of this artery and the blood flow velocity were measured before and after local injection of diltiazem (0.5 mg).

Coronary artery diameter assessment: After successful angioplasty, the diameter of the epicardial coronary artery was measured in the nonstenotic contralateral coronary artery before and after intracoronary administration of diltiazem. Care was taken to measure the diameter 2 mm ahead from the tip of the Doppler catheter (site of the sample volume). For these measurements, 2 perpendicular angiographic projections were used. Angiograms before and after diltiazem were obtained in identical transversal and sagittal inclinations with constant focus-object and object-image intensifier distances. Images were acquired on a Polytron® 1000 system (Siemens, Erlangen, Federal Republic of Germany) after hand injections of a nonionic, low-osmolar contrast agent (Omnipaque®, Nycomed, Oslo, Sweden). End-diastolic angiographic views were analyzed by 2 independent and experienced operators unaware of pretreatment medication. Diameters were measured 3 times in each projection, resulting in 12 measurements from which the mean value was calculated. Measurement of the diameter was performed with the special stenosis protocol of the Polytron® 1000, and the external diameter of the guiding catheter was used for calibration. The stenosis protocol program has been validated before in phantoms, showing a geometric resolution that goes down to 0.6 mm with reliable discrimination of 0.1 mm differences.[8]

Doppler measurements: An anular 20 MHz crystal, end-mounted on the tip of a 3Fr over-the-wire catheter was connected to a Doppler velocimeter (Model PDV-20®, Schneider Shiley, Zurich, Switzerland). The Doppler catheter was advanced over a 0.010-inch J-tip floppy guidewire (Schneider Shiley) into the proximal part of the nonstenotic coronary artery. The exact site of the Doppler crystal, visible by its radiopaque marker, was recorded as a reference for further assessments of the diameter. The Doppler signal was considered stable when exaggerated respiration or coughing was unsuccessful in permanently altering the velocity signal; before each measurement, velocity calibration signals were recorded. At least 5 minutes after the control angiogram, the mean and phasic baseline coronary blood flow velocity signals were recorded simultaneously with arterial pressure and a 5-lead electrocardiogram (Mingograf 7®, Siemens). As soon as the signal was stable for >2 minutes, a 1 ml bolus of papaverine hydrochloride (10 mg in 0.9% saline solution) was hand injected through the central lumen of the Doppler catheter. As soon as the Doppler signal returned to baseline and remained stable for >1 minute, 500 μg of diltiazem were hand injected as a 1 ml bolus in 0.9% saline solution through the central lumen of the Doppler catheter. Doppler signals were recorded continuously for 5 minutes. Thereafter a second dose of 10 mg of papaverine was administered exactly as before. The baseline and maximal phasic and mean coronary blood flow signals were used for the calculation of the coronary hemodynamic parameters before and after diltiazem.

Calculations: Coronary blood flow velocity and epicardial coronary artery diameter data were combined to calculate blood flow. The velocity-area index, defined as coronary blood flow velocity · π · $(D/2)^2$, with D representing mean arterial diameter of the 2 angiographic projections, was considered as a measure for coronary blood flow across the segment under study.[9]

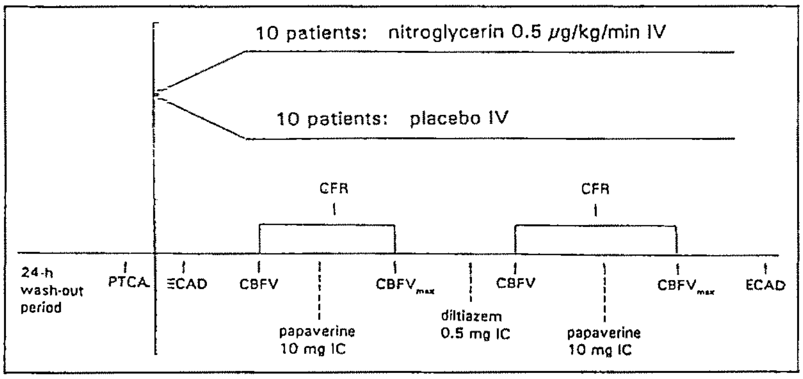

FIGURE 1. Flow chart of study protocol. CBFV = coronary blood flow velocity; CBFV$_{max}$ = maximum CBFV; CFR = coronary flow reserve; ECAD = epicardial coronary artery diameter; IC = intracoronary; PTCA = percutaneous transluminal coronary angioplasty.

TABLE I Patient Characteristics and Hemodynamic Changes After Intracoronary Diltiazem

Pt. No.	Age (yr)	Pretreatment (N/P)	Ejection Fraction (%)	Artery	$ECAD_b$	$ECAD_a$	$CBFV_b$	$CBFV_a$	CBF_b	CBF_a	CFR_b	CFR_a
1	63	P	73	LAD	1.3	1.7	3.8	4.6	7.0	10.2	2.1	1.6
2	60	P	86	LC	2.9	3.1	0.7	0.7	4.4	5.6	1.7	1.4
3	47	N	78	LC	2.0	3.0	2.5	1.9	7.6	13.6	1.9	2.0
4	32	P	74	LC	2.7	3.0	0.6	0.7	3.6	5.2	3.0	2.6
5	49	N	82	LC	2.3	2.5	0.9	0.9	3.8	4.4	2.5	2.4
6	62	P	79	LAD	1.6	2.6	1.6	1.8	8.2	10.0	2.2	1.7
7	61	P	67	LC	2.6	3.1	2.6	2.4	14.0	17.8	2.5	2.3
8	41	P	62	LAD	2.6	2.8	1.4	1.4	7.2	8.8	1.9	1.6
9	44	N	63	LAD	3.1	3.3	0.4	0.4	2.8	3.2	6.1	6.0
10	51	N	65	LC	3.0	3.1	0.6	0.6	3.8	5.0	5.7	5.5
11	53	N	87	LAD	2.7	2.9	1.4	1.4	9.0	10.2	4.0	3.9
12	65	P	77	LC	2.3	2.5	0.8	1.1	3.4	5.4	2.5	2.1
13	40	P	74	LAD	1.9	2.1	1.6	1.5	4.4	5.2	2.2	2.0
14	67	N	61	LAD	2.7	2.9	1.4	1.3	8.0	8.6	2.6	2.9
15	62	P	66	LAD	2.2	2.4	2.3	2.7	9.0	12.6	1.7	1.5
16	47	N	67	LC	2.6	2.7	2.2	2.5	12.0	14.6	1.5	1.4
17	52	N	60	LC	3.3	3.5	1.5	1.8	12.8	16.4	2.7	2.2
18	61	N	80	LC	2.6	2.6	2.1	2.6	11.2	13.8	2.8	2.4
19	63	N	74	LC	2.2	2.7	1.9	1.9	7.0	11.2	1.9	2.0
20	65	P	76	LAD	2.0	2.0	0.8	1.0	2.6	3.4	6.1	4.3
Mean ± SEM	54.2 ± 2.2		72.6 ± 2.0		2.5 ± 0.1	2.7 ± 0.1*	1.6 ± 0.2	1.7 ± 0.2	7.0 ± 0.5	9.2 ± 0.6*	2.9 ± 0.3	2.6 ± 0.3

*$p < 0.05$ after versus before diltiazem.

a = after diltiazem; b = before diltiazem; CBF = coronary blood flow (kHz · mm^2); CBFV = coronary blood flow velocity (kHz); CFR = coronary flow reserve; ECAD = epicardial coronary artery diameter (mm); LAD = left anterior descending; LC = left circumflex; N = nitrates; P = placebo; SEM = standard error of the mean.

TABLE II Subgroup Analysis According to Pretreatment Group

	Placebo (n = 10)			Nitrates (n = 10)		
	Before Diltiazem	After Diltiazem	p Value	Before Diltiazem	After Diltiazem	p Value
ECAD (mm)	2.3 ± 0.2	2.5 ± 0.2	0.0001	2.6 ± 0.1	2.9 ± 0.1	0.02
CBFV (kHz)	1.6 ± 0.3	1.8 ± 0.4	NS	1.5 ± 0.2	1.5 ± 0.2	NS
$CBFV_{max}$ (kHz)	3.8 ± 0.7	3.4 ± 0.6	0.005	3.9 ± 0.4	3.8 ± 0.4	NS
CBF	6.4 ± 0.6	8.4 ± 0.7	0.0001	7.8 ± 0.6	10.2 ± 0.7	0.003
CFR	2.6 ± 0.4	2.1 ± 0.3	0.008	3.2 ± 0.5	3.1 ± 0.5	NS

Values are mean ± SEM.

$CBFV_{max}$ = maximal mean CBFV after papaverine; other abbreviations as in Table I.

Coronary flow reserve was calculated as the quotient of mean coronary blood flow velocity after papaverine versus baseline.[10]

Statistical methods: Paired *t* tests were used for comparison in which each patient served as his own control. Unpaired *t* tests were used for between-group comparisons. A p value <0.05 was considered significant. All values are expressed as mean ± standard error of the mean.

RESULTS

Patients: Of 25 patients randomized, 20 were included in this study; their main characteristics are listed in Table I. No significant differences were observed between treatment groups. Exclusions before administration of the study drug were due to administration of vasoactive drugs (2 patients), failed angioplasty (1) and technical problems (1). Another patient was excluded because of temporary second-degree atrioventricular block after administration of diltiazem.

Effects on epicardial coronary artery diameter: The intracoronary administration of diltiazem resulted in a 10% increase in diameter in both the presence (2.64 ± 0.13 to 2.91 ± 0.10 mm; p = 0.02) and absence (2.31 ± 0.15 to 2.54 ± 0.16 mm; p = 0.0001) of nitrates (Tables I and II).

Effects on coronary blood flow velocity: This parameter did not change significantly after administration of diltiazem (1.56 ± 0.19 before vs 1.66 ± 0.22 kHz after; p = 0.11) (Table I). Likewise, no difference in velocity response was observed when both pretreatment groups were analyzed separately (Table II).

Effects on coronary blood flow: After diltiazem, coronary blood flow increased 31% (p = 0.0001) (Table I). Similar increases were observed in patients pretreated with nitrates (30%; p = 0.003) and placebo

(31%; p = 0.0003) (Table II). Coronary blood flow increased in all patients, but varied from 12 to 81%. No correlation was found between coronary blood flow response and baseline diameter or flow velocity.

Effects on coronary flow reserve: Administration of intracoronary diltiazem resulted in a 10% decrease in coronary flow reserve in all patients (p = 0.004) (Table I). Subgroup analysis showed that this decline was limited to patients pretreated with placebo (19%; p = 0.0008); in patients pretreated with nitrates, no significant changes in measurements before and after diltiazem were observed (−3%; p = not significant [NS]) (Table II). Individual coronary flow reserve responses in patients pretreated with placebo and nitrates are depicted in Figure 2.

Effects on heart rate and blood pressure: Intracoronary administration of diltiazem did not induce any change in heart rate (70 ± 2.8 before vs 69 ± 2.6 beats/min after; p = NS) or systolic blood pressure (128 ± 6.5 before vs 126 ± 5.7 mm Hg after; p = NS) (Table I). No significant changes in these parameters were observed in either pretreatment subgroup.

Side effects: Diltiazem induced a second-degree atrioventricular block in 1 patient; sinus rhythm returned to normal spontaneously within 10 minutes. The patient was excluded from analysis.

DISCUSSION

This study demonstrates that in nonpremedicated patients, intracoronary administration of the calcium antagonist diltiazem increases epicardial coronary diameter and coronary flow without any change in heart rate or blood pressure. These effects were observed in patients pretreated with either placebo or nitrates. Coronary vasodilation diameter correlates well with previous findings. After pretreatment with nitrates, increases in diameter of 9 and 6% were observed after intravenous and intracoronary diltiazem, respectively.[6] After systemic administration of the dihydropyridine-type calcium antagonist, nisoldipine, epicardial coronary artery diameter increased by 10% in the absence of nitrates.[11] Epicardial artery vasodilation after calcium entry blockade appears to be independent of pretreatment with nitrate. Calcium antagonists appear to be less effective than treatment with intracoronary nitrocompounds. Previously, in the same model we assessed the vasodilator action of Sin 1, the active metabolite of the nitrocompound molsidomine.[12] Sin 1 increased the epicardial coronary diameter by 26% compared with a 10% increase for diltiazem in the present study.

The increase in coronary blood flow correlates well with previous findings. Intracoronary nifedipine (0.1 mg) resulted in a 70% increase in blood flow, as measured by the coronary sinus thermodilution technique.[13] In view of the known limitations of this technique, especially for the measurement of small flow changes[14] we estimated coronary flow from a combination of quantitative angiography and Doppler measurements.[9] Blood flow increase after diltiazem appeared to be due to a dual action, namely dilatation of both resistance and epicardial capacitance vessels. Coronary blood flow response was consistent in all patients and was independent of pretreatment with nitrate. These results compare favorably with previous work with intracoronary nitrocompounds in which no significant changes in coronary blood flow were observed after a 0.5 mg Sin-1 bolus.[14]

Intracoronary diltiazem resulted in a small but significant decrease in coronary flow reserve. When subgroup analysis was performed, the reduction in flow reserve appeared to be limited to patients pretreated with placebo, in agreement with the findings of Rossen et al.[6] The mechanism by which diltiazem reduced the flow reserve response could be either by "raising the

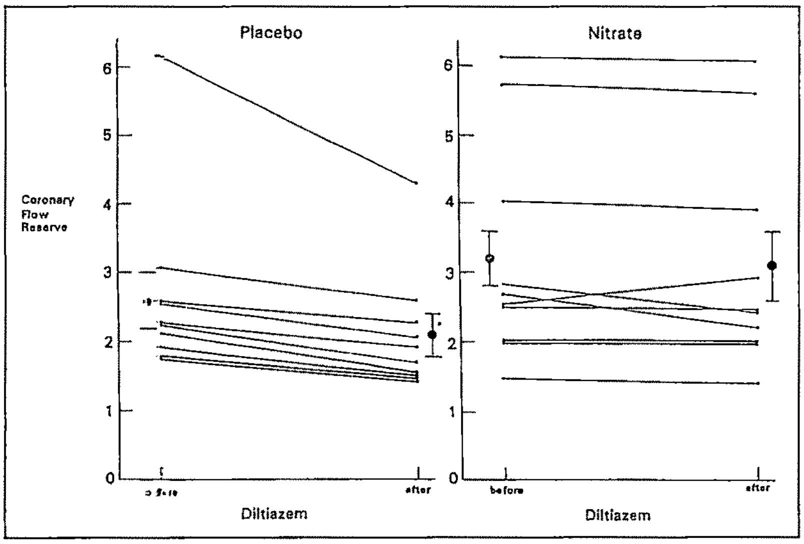

FIGURE 2. Coronary flow reserve responses after diltiazem for individual patients. *Left,* patients pretreated with placebo; *right,* patients pretreated with nitrates. Mean ± standard error of the mean for values before and after diltiazem are indicated. *p <0.05.

floor" or "lowering the ceiling." Indeed, at the time of the second papavarine injection, coronary blood flow at baseline may be increased (epicardial vasodilation without change in blood flow velocity). In such situation, although papaverine increased blood flow to the same maximal level as before diltiazem, the ratio will decrease. Although this mechanism offers a plausible hypothesis it does not explain all findings (e.g., absence of decrease after nitrates, and larger percent decrease of flow velocity reserve with respect to the percentage of epicardial vasodilation in patients treated with placebo). Therefore, the lowering the ceiling mechanism (i.e., a decrease in maximal blood flow after the second papaverine injection) must also play a role. In experiments with animals, blunting of the hyperemic response after brief coronary occlusions by diltiazem and dihydropyridine-type calcium antagonists was observed.[15,16] Merrill et al[17] studied the effect of nifedipine on adenosine-induced hyperemic flow. Nifedipine attenuated the hyperemic response after adenosine, and this effect appeared reversible. In the present study, no attempt was made to reverse the effect of diltiazem, because it was considered unsafe to increase the dose of papaverine because of potential complications.[18,19] The exact mechanism by which diltiazem could reduce papaverine-induced hyperemia remains unclear. Besides the possibility of direct inhibition of the effect of papaverine on resistance vessels, another possible explanation exists. Indeed, although systemic hemodynamics remained unchanged diltiazem could have caused a regional negative inotropic effect resulting in unpaired diastolic relaxation and impairment of maximal coronary blood flow.

In conclusion, intracoronary administration of diltiazem (0.5 mg) produced significant dilatation of the epicardial arteries and increased blood flow in the intact coronary circulation of humans without systemic effects. Coronary flow reserve decreased, but only in the absence of pretreatment with nitrates. The decrease in this parameter appears to be due to increased baseline as well as decreased maximal blood flow. Concomitant administration of nitrates by an unknown mechanism inhibits this effect on flow reserve. Whether a reduction of flow reserve in the setting of obstructive coronary disease (by reducing a 'coronary steal' phenomenon) represents a beneficial mechanism remains to be proven.

Acknowledgment: The technical assistance of J. Adams and C. Borgers, and the secretarial help of S. Van Roey are greatly appreciated. We thank R. Scheldewaert, MD, and I. Thijssen, MD, for providing diltiazem and valuable help in the preparation of the study protocol.

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Regional Myocardial Perfusion and Metabolism Assessed by Positron Emission Tomography in Children with Kawasaki Disease and Significance of Abnormal Q Waves and Their Disappearance

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To clarify the significance of newly appearing abnormal Q waves and their disappearance in patients with Kawasaki disease, regional myocardial perfusion and glucose metabolism at rest in the fasting condition were assessed by positron emission tomography (PET) with ^{13}N-ammonia and ^{18}F-fluorodeoxyglucose (FDG), and regional wall motion by left ventriculography in regions with persistent and transient abnormal Q waves in 14 patients. PET identified 3 groups of abnormal myocardial segments: segments with hypoperfusion without increased FDG uptake, those with hypoperfusion and increased FDG uptake, and those with normal perfusion and increased FDG uptake. Almost all the segments with persistent or transient abnormal Q waves had abnormal PET findings. PET demonstrated evidence of metabolic activity in 57% of segments with persistent abnormal Q waves and 67% of those with transient abnormal Q waves. Regional wall motion, scored from 0 (normal) to 4 (dyskinesia), was not significantly different between segments with persistent and transient abnormal Q waves (2.3 ± 1.3 vs 2.2 ± 1.2). The persistence of abnormal Q waves on serial electrocardiograms was significantly shorter in metabolically active than in inactive segments (19 ± 17 vs 92 ± 27 months). In conclusion, in patients with Kawasaki disease, the new appearance of abnormal Q waves is a reliable clue to the presence of ischemic myocardial injury and a high proportion of them are associated with metabolically active myocardial regions. The disappearance of abnormal Q waves does not necessarily mean the normalization of regional myocardial perfusion, metabolism or function, and their early disappearance may imply "viability" in the associated myocardial region.

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Coronary artery lesions occur in about 20% of patients with Kawasaki disease,[1,2] and some of them then develop myocardial ischemia.[3] Coronary artery lesions resulting from Kawasaki disease are characteristic in that there are a large number of patients with asymptomatic myocardial infarction.[3] Because the detection of elevated enzyme levels is impossible in these patients, the diagnosis of myocardial infarction is usually made by the new appearance of abnormal Q (abnormally deep Q) waves on the electrocardiogram, and such Q waves often disappear in the subsequent course of the illness. However, little is known concerning the ischemic myocardial injury in regions with such Q waves or in regions showing disappearance of them.

In recent years, the in vivo evaluation of regional myocardial perfusion and metabolism has become feasible with the advent of positron emission tomography (PET),[4–8] and its usefulness in the assessment of myocardial ischemia has been reported in adults.[9,10] However, there have been no studies so far to assess myocardial perfusion or metabolism using PET in patients with Kawasaki disease.

In the present study, to clarify the significance of newly appearing abnormal Q waves and their disappearance in patients with Kawasaki disease, regional myocardial perfusion and glucose metabolism were assessed by PET with ^{13}N-ammonia and ^{18}F-fluorodeoxyglucose (FDG), and regional wall motion by left ventriculography in regions with abnormal Q waves and in regions showing the Q-wave disappearance.

METHODS

Patients: We studied 14 patients (10 male and 4 female children, aged 3 to 14 years [mean 7.6]) with coronary artery lesions resulting from Kawasaki dis-

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ease. All patients had stenotic lesions of coronary arteries confirmed by selective coronary arteriography. The time from the onset of Kawasaki disease to the PET study ranged from 6 to 163 months (mean 67). Written informed consent was obtained from the parents of each child before the study.

Positron emission computed scanning: PET scanning was performed using a whole-body, multislice positron tomograph (Positologica III, Hitachi).[11] The spatial resolution was 7.6 mm (full width at half maximum) at the center of the field. Nitrogen-13 and fluorine-18 were produced using a small cyclotron (SYPRIS 325, Sumitomo) as previously reported.[10,12,13] Before each tomographic study, a transmission scan using a rotating germanium 68/gallium 68 standard plate was performed for measurement of the attenuation factor. Patient positioning for each study was aided by marking the patient's chest with a felt pen and aligning the marks with the reference light beam of the tomograph. While the patient was lying on the bed, ^{13}N-ammonia (0.4 mCi/kg) was injected intravenously and 3 minutes after the injection, the first scan was performed for 5 minutes. This was followed immediately by the second scan that was performed for 8 minutes to obtain interpolating images. These 2 scans provided a total of 14 contiguous transverse slices at 8 mm intervals. Myocardial images were included in 5 to 7 slices of the 14 obtained. The FDG study was performed within 1 week of the ^{13}N-ammonia study. There were no changes in clinical status in any of the patients during the interval. Patients fasted for ≥5 hours before the FDG study. FDG (0.1 mCi/kg) was injected at rest and 2 emission scans of 8 minutes' duration were taken 60 minutes after the injection to obtain 14 contiguous slices.

Before injection of FDG, venous blood was withdrawn for measurement of plasma levels of glucose, free fatty acids and insulin to detect possible differences in plasma substrate levels among the patients.

Image analysis: The PET images were reconstructed with a Shepp & Logan filter convoluted with a 2 mm Gaussian function after attenuation correction. The spatial resolution after reconstruction was about 9.0 mm (full width at half maximum) at the center of the field.

Regional myocardial perfusion images were semiquantitatively assessed by the circumferential profile analysis of 3 transverse slices (upper, middle and lower) as previously reported.[10,12] The PET study provided 5 to 7 myocardial slices at 8 mm intervals. The lowest slice showing decreased activity in the center corresponding to the left ventricular cavity was determined as the lower slice. The middle and upper slices were determined as every second slice above the lower slice.[10,12] The left ventricular myocardium was divided into 5 segments (septal, anterior, apical, lateral and inferior). Segments with perfusion below the normal range (mean ± 2 standard deviation value of 12 normal subjects) covering ≥30° of the profiles were defined as having hypoperfusion and the other segments were defined as having normal perfusion.[10,12] The 3 slices selected for the circumferential analysis and the 5 myocardial segments are shown schematically in Figure 1.

Regional FDG uptake was measured as percent injected dose per 100 ml tissue in each segment and was assessed by the circumferential profile analysis as previously reported.[12,13] Segments with FDG uptake above the normal range (mean ± 2 standard deviation value of 8 normal subjects in the fasting state) covering ≥30° of the profiles were considered to have increased FDG uptake and the other segments to have no increase in FDG uptake. The upper limit of the normal range was 0.7% injected dose per 100 ml tissue in septal, anterior and apical segments and 0.85 in lateral and inferior segments.[13]

Electrocardiographic analysis: Electrocardiograms were recorded at least once a month from the onset of Kawasaki disease until the day of the PET scanning.

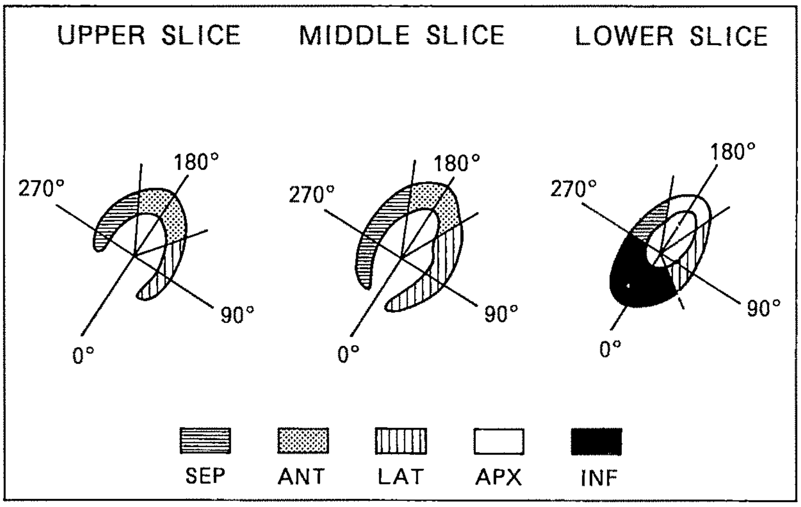

FIGURE 1. Schematic representation of 3 transverse tomographic slices selected for the circumferential profile analysis and 5 myocardial segments. ANT = anterior segment; APX = apical segment; INF = inferior segment; LAT = lateral segment; SEP = septal segment.

TABLE I Clinical Data and Tomographic Findings in 14 Patients

Pt. No.	Age (yr) & Sex	CAG			Abnormal Q on ECG	PET Perfusion/FDG Uptake/Wall Motion Score				
		AD	CX	RC	Site/Persistent or Transient/Persistence (mos)	SEP	ANT	APX	LAT	INF
1	7M	100	50	90	V_3,V_4/P/79	→/−/1	↓/−/2	↓/−/4	→/−/1	→/−/0
2	7M	N	N	SS	III,aVF/P/77	→/−/0	→/−/0	↓/−/1	→/−/2	↓/−/2
3	13M	A	N	SS	II,III,aVF/P/140	→/−/0	→/−/0	↓/−/1	→/−/0	↓/−/4
4	8M	A	99	90	I,aVL/T/86	→/−/0	→/−/0	→/−/0	↓/−/3	↓/−/1
5	8F	N	N	SS	II,III,aVF/T/80	→/−/0	→/−/0	→/−/0	→/−/0	↓/−/2
6	3M	100	A	A	V_{1-4},I,aVL/P/3	↓/+/2	↓/+/3	↓/+/1	→/−/0	→/−/0
7	3M	N	75	SS	II,III,aVF/P/34	→/−/0	→/−/0	→/−/0	↓/+/3	↓/+/3
8	10F	A	75	SS	No abnormal Q	→/−/0	→/−/0	→/−/0	↓/+/1	↓/+/2
9	14M	N	SS	SS	III,aVF/T/31	→/−/0	→/−/0	→/−/0	→/+/2	→/+/2
10	8M	75	N	SS	III,aVF/T/37	→/−/0	→/−/0	→/−/0	→/−/0	→/+/3
11	12M	A	A	SS	No abnormal Q	→/−/0	→/−/0	→/−/0	→/−/0	→/+/1
12	3F	90	50	SS	I,aVL/T/1; II,III,aVF/T/5	→/−/0	→/−/1	→/−/0	→/−/0	→/+/3
13	7M	90	N	N	No abnormal Q	→/−/0	→/−/0	→/−/0	→/−/0	→/−/0
14	3F	50	A	A	No abnormal Q	→/−/0	→/−/0	→/−/0	→/−/0	→/−/0

A = aneurysm; AD = left anterior descending artery; ANT = anterior segment; APX = apical segment; CAG = coronary arteriography (number in CAG column; percent reduction in diameter in localized stenosis); CX = left circumflex artery; ECG = electrocardiogram; FDG = ^{18}F-fluorodeoxyglucose (−, no increase in FDG uptake; +, increased FDG uptake); INF = inferior segment; LAT = lateral segment; N = normal findings; P = persistent abnormal Q waves; PET = positron emission tomography (→, normal perfusion; ↓, hypoperfusion); RC = right coronary artery; SEP = septal segment; SS = segmental stenosis; T = transient abnormal Q waves.

Myocardial infarction was defined as the new appearance of abnormal Q (abnormally deep Q) waves during this period. Abnormal Q waves were defined as Q waves with a depth greater than the 98 percentile value for normal children (0.3 mV in lead I, 0.4 mV in leads II, aVL and aVF, 0.5 mV in lead III, 0.2 mV in leads V_1 to V_3, and 0.6 mV in leads V_4 to V_6),[14,15] or QS waves. Septal infarction was diagnosed when there were new abnormal Q waves in leads V_1 and V_2, anterior infarction when new Q waves appeared in leads V_3 to V_5, lateral infarction when they were present in ≥2 of leads I, aVL and V_6, and inferior infarction when they appeared in ≥2 of leads II, III and aVF.

Analysis of coronary arteriography and regional wall motion: Selective coronary arteriography and left ventriculography in both the right and left anterior oblique projections were performed within 30 days (mean interval 13.5) before or after the PET scan. None of the patients showed any changes in their clinical status or electrocardiographic findings during the interval. Stenotic lesions of the coronary arteries were defined as occlusion, segmental stenosis or localized stenosis as recommended by the Kawasaki Disease Research Committee of the Japanese Ministry of Health and Welfare.[16] According to the committee, occlusion is defined as 100% obstruction. Segmental stenosis is

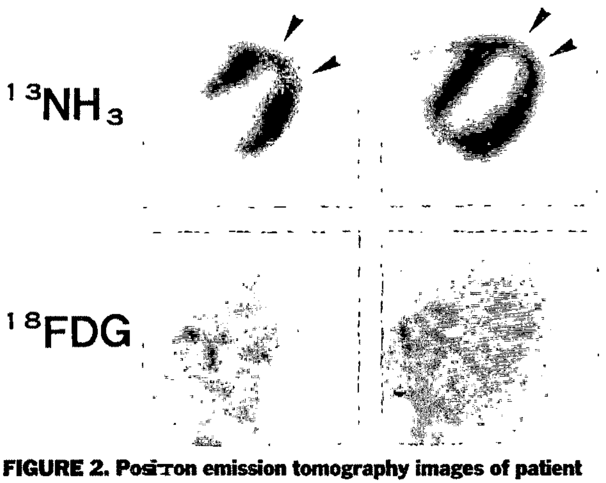

FIGURE 2. Positron emission tomography images of patient 1. *Upper and lower panels* on the *left and right* are transverse slices at the same level. *Upper panels* are ^{13}N-ammonia (^{13}NH$_3$) images showing hypoperfusion in the anterior and apical segments *(arrows)*. *Lower panels* are ^{18}F-fluorodeoxyglucose (^{18}FDG) images showing no increase in FDG uptake. These segments are representative of group A.

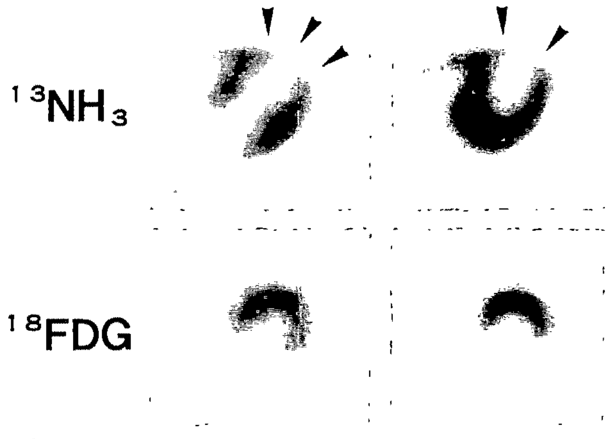

FIGURE 3. Positron emission tomography images in patient 6. *Upper and lower panels* on the *left and right* are transverse slices at the same level. *Upper panels* are ^{13}N-ammonia (^{13}NH$_3$) images showing hypoperfusion in the septal, anterior and apical segments *(arrows)*. *Lower panels* are ^{18}F-fluorodeoxyglucose (^{18}FDG) images showing increased FDG uptake in the same segments. These segments are representative of group B.

TABLE II Plasma Levels of Glucose, Free Fatty Acids, and Insulin at the Time of the ^{18}F-Fluorodeoxyglucose (FDG) Study

	Glucose (mg/dl)	Free Fatty Acids (μEq/liter)	Insulin (μU/ml)
Patients: FDG(+) (n = 7)	81 ± 14	1,368 ± 1,066	3.6 ± 2.3
Patients: FDG(−) (n = 7)	84 ± 6	1,628 ± 582	2.7 ± 1.9
Normal subjects (n = 8)	90 ± 8	1,065 ± 699	3.5 ± 1.8

Values are mean ± standard deviation.
FDG(+) = increased FDG uptake; FDG(−) = no increase in FDG uptake.

TABLE III Correlation Between Abnormal Q Waves and Positron Emission Tomographic Findings

	PET Findings (^{13}N-ammonia perfusion/FDG uptake)				
Abnormal Q Waves on ECG	→/− Normal	→/+ Group C	↓/+ Group B	↓/− Group A	Total
Persistent	1	0	3	3	7
Transient	1	3	0	2	6
No abnormal Q	37	2	3	1	43
Total	39	5	6	6	56

Values shown are the number of myocardial segments.
ECG = electrocardiogram; FDG = ^{18}F-fluorodeoxyglucose (−, no increase in FDG uptake; +, increased FDG uptake); PET = positron emission tomographic (→, normal perfusion; ↓, hypoperfusion).

defined as severe narrowing over a long segment of a coronary artery, which forms a braidlike lesion associated with multiple tortuous vessels.[16,17] Localized stenosis is defined as a discrete narrowing of a coronary artery. Regional wall motion in each segment was assessed visually on the basis of left ventriculography by 3 experienced observers who were unaware of the results of PET or electrocardiography, and was scored as follows: normal = 0, mild hypokinesia = 1, severe hypokinesia = 2, akinesia = 3 and dyskinesia = 4.

Statistical analysis: Values are reported as mean ± standard deviation. One-way analysis of variance with multiple comparisons (Dunn's method) was used to compare variables. To compare proportions, Fisher's exact test was used. Probability values of <0.05 were considered statistically significant.

RESULTS

The clinical data and PET findings of the 14 patients are summarized in Table I. New abnormal Q waves appeared in 10 patients and the abnormal Q waves disappeared in 5 of them during follow-up. A diagnosis of myocardial infarction, which was based on the new appearance of abnormal Q waves, was made in 13 myocardial regions in these 10 patients (1 septal, 2 anterior, 3 lateral and 7 inferior infarcts). Signs or symptoms accompanying the appearance of abnormal Q waves were observed in only 1 patient (no. 1). In the remaining 9 patients, routine electrocardiograms revealed the development of abnormal Q waves, but there were no signs or symptoms. Therefore, asymptomatic myocardial infarction was the diagnosis in these 9 patients. According to the PET findings, all the myocardial segments were classified into the following 4 groups: segments with hypoperfusion and no increase in FDG uptake (group A) (Figure 2), those with hypoperfusion and increased FDG uptake (group B) (Figure 3), those with normal perfusion and increased FDG uptake (group C) (Figure 4), and those with normal perfusion and no increase in FDG uptake (normal group).

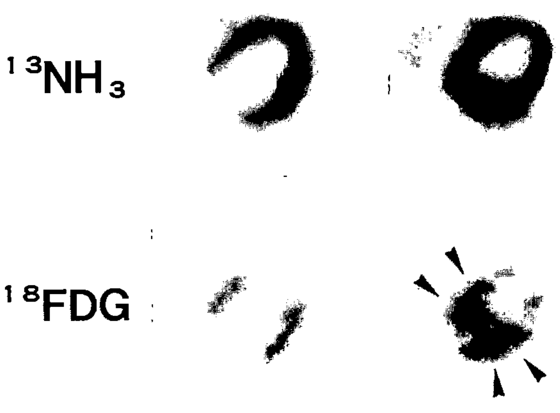

FIGURE 4. Positron emission tomography images in patient 10. *Upper and lower panels* on the *left and right* are transverse slices at the same level. *Upper panels* are ^{13}N-ammonia (^{13}NH$_3$) images showing normal perfusion and *lower panels* are ^{18}F-fluorodeoxyglucose (^{18}FDG) images showing increased FDG uptake in the inferior segment *(arrows)*. The inferior segment in this patient is representative of group C.

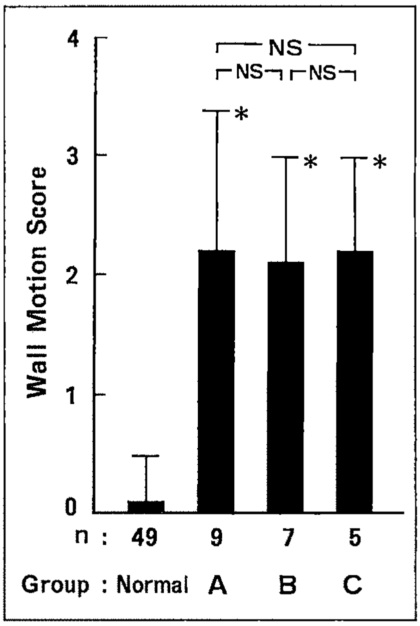

FIGURE 5. Regional wall motion scores in myocardial segments of groups A to C and in normal segments. The heights of the *bars* indicate mean values; *brackets* represent standard deviation. n = number of myocardial segments in each group; NS = not significantly different; *p <0.001 versus normal segments.

Table II shows plasma levels of glucose, free fatty acids and insulin in patients and normal subjects. There were no significant differences in plasma levels of these substances among patients with and without increased FDG uptake and normal subjects.

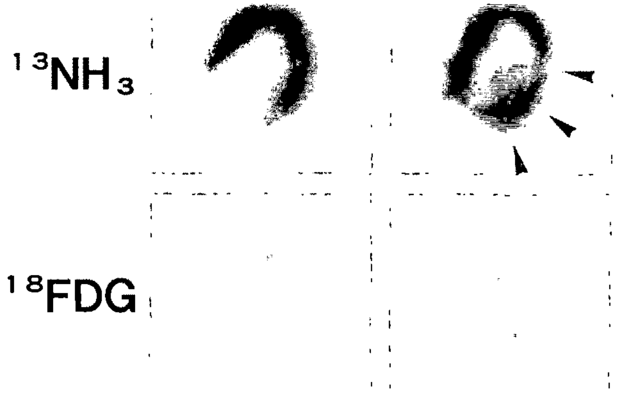

FIGURE 6. Positron emission tomography images in patient 4. ***Upper and lower panels*** **on the** ***left and right side*** **are transverse slices at the same level.** ***Upper panels*** **are ^{13}N-ammonia ($^{13}NH_3$) images showing hypoperfusion in the lateral and inferior segments** ***(arrows).*** **Lower panels are ^{18}F-fluorodeoxyglucose (^{18}FDG) images showing no increase in FDG uptake. These segments are typical of group A.**

Figure 5 shows the relation between the PET findings and regional wall motion. Normal myocardial segments had significantly better wall motion than those in groups A, B or C. There were no significant differences in wall motion scores among groups A, B and C.

The relation between abnormal Q waves and the PET findings is shown in Table III. Almost all myocardial segments with persistent or transient abnormal Q waves had abnormal PET findings. The proportion of group A segments was not significantly different between those with persistent and those with transient abnormal Q waves.

Figures 4 and 6 show the PET findings in patients with transient abnormal Q waves. Electrocardiograms of the same patients are shown in Figures 7 and 8, respectively.

Table IV shows the relation between the persistence of abnormal Q waves (intervals from appearance to PET scanning in patients with persistent abnormal Q waves and interval from appearance to disappearance in patients with transient abnormal Q waves) and the PET findings. The persistence of abnormal Q waves was significantly shorter in metabolically active segments (groups B, C, and the normal group) than in inactive segments (group A).

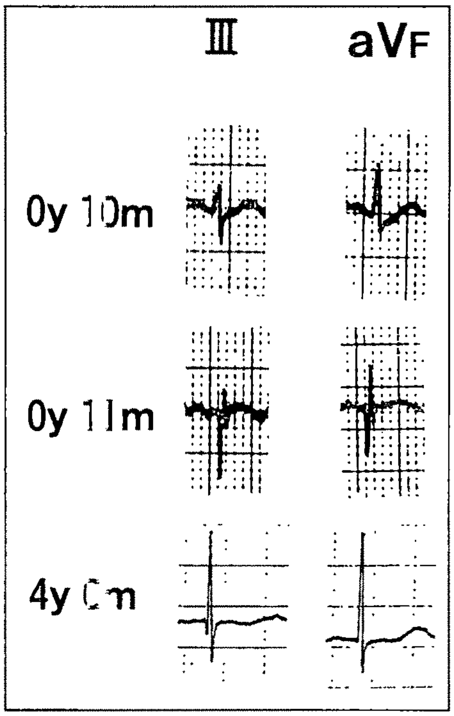

FIGURE 7. Serial electrocardiograms (leads III and aVF) from same patient as in Figure 4 (no. 10). At onset of Kawasaki disease (0y 10m), there were no abnormal Q waves ***(upper panels).*** **At age 11 months (0y 11m) (1 month after the onset), abnormal Q waves appeared in these leads** ***(middle panels)*** **without clinical signs or symptoms. At age 4 years (4y 0m) (37 months after the appearance), abnormal Q waves disappeared** ***(lower panels).*** **This patient had an asymptomatic inferior myocardial infarction with transient abnormal Q waves.**

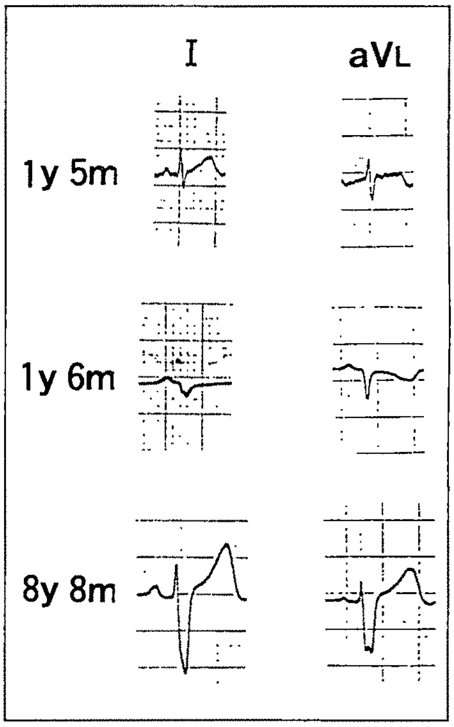

FIGURE 8. Serial electrocardiograms (leads I and aVL) from the same patient as in Figure 6 (no. 4). At the onset of Kawasaki disease (1y 5m), there were no abnormal Q waves ***(upper panels).*** **At the age of 1 year and 6 months (1y 6m) (1 month after the onset), abnormal Q waves appeared in these leads** ***(middle panels)*** **without clinical signs or symptoms. At 8 years of age (8y 8m) (86 months after the appearance), abnormal Q waves disappeared** ***(lower panels).*** **This patient had an asymptomatic lateral myocardial infarction with transient abnormal Q waves.**

The relation between abnormal Q waves and regional wall motion is shown in Figure 9. Myocardial segments without abnormal Q waves had significantly better wall motion than segments with persistent or transient abnormal Q waves. The wall motion score was not significantly different between segments with persistent abnormal Q waves and those with transient abnormal Q waves.

DISCUSSION

In the present study, PET identified 3 types of abnormal myocardial segments (groups A to C). Segments in group B (hypoperfusion with increased FDG uptake) are considered to be ischemic but metabolically active, i.e., tomographically "viable" segments. Segments in group A (hypoperfusion without increased FDG uptake) may represent ischemic and metabolically inactive, i.e., tomographically "non-viable" or scar regions. Segments in group C showed increased FDG uptake with normal perfusion and also had significantly reduced wall motion (Figure 5). It is difficult to explain the potential reason or mechanism for the group C finding. However, the same PET finding was frequently observed in adult patients with subendocardial or non-Q-wave myocardial infarction.[18] The group C finding in the present study may also represent subendocardial myocardial ischemia which may occur asymptomatically. This finding was observed in myocardial regions with transient abnormal Q waves or non-Q-wave regions, but not in regions with persistent abnormal Q waves (Table III). We performed the FDG study under the fasting condition to delineate metabolically abnormal areas by suppressing FDG uptake in the normal myocardium. Myocardial segments with this type of ischemic injury, i.e., normal perfusion but abnormal metabolism, can be identified in the fasting state but not in the postprandial state.

No significant differences in plasma levels of glucose, free fatty acids and insulin between the patients with and without increased FDG uptake (Table II) indicate that the increased FDG uptake observed in the present study did not result from changes in the plasma levels of these substances.

TABLE IV Relation Between Persistence of Abnormal Q Waves and Positron Emission Tomographic Findings

PET Findings	Metabolically Active Segments (groups B and C, and the normal group)	Metabolically Inactive Segments (group A)
Persistence of abnormal Q waves (mos) on ECG	18.5 ± 17.1	92.4 ± 26.8*

*p <0.01 versus metabolically active segments.
Values are mean ± standard deviation.
ECG = electrocardiogram; PET = positron emission tomographic.

The present study revealed that new and asymptomatic abnormal Q waves were almost always associated with both abnormal PET findings (Table III) and reduced wall motion (Figure 9), whether or not they persisted or eventually disappeared. In addition, evidence of metabolic activity was demonstrated in 62% of myocardial regions with such abnormal Q waves. These findings indicate that the new appearance of abnormal Q waves is a reliable clue to the presence of asymptomatic regional myocardial ischemic injury in patients with Kawasaki disease, and that a high proportion of such Q waves are associated with tomographically viable myocardial regions.

The disappearance of abnormal Q waves is not an unusual finding in patients with Kawasaki disease as well as in adult patients with myocardial infarction.[19-23] In some previous reports, the disappearance of abnormal Q waves has been attributed to a smaller infarct size[19] and related to a more favorable prognosis,[20] whereas others have failed to note any association with a better prognosis.[21-23] However, there have been no studies so far concerning myocardial perfusion or metabolism in regions showing the disappearance of abnormal Q waves. In the present study, transient and persistent abnormal Q waves were associated with a similar number of tomographically abnormal myocardial segments, and also with a similar number of metabolically inactive (group A) segments (Table III). In addition, myocardial segments with transient and persistent abnormal Q waves showed similarly reduced

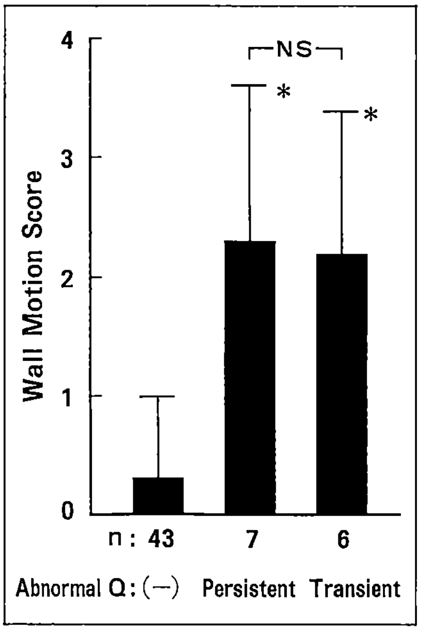

FIGURE 9. Regional wall motion scores in myocardial segments with persistent and transient abnormal Q waves and in segments without abnormal Q waves. The heights of the *bars* indicate mean values, and *brackets* represent standard deviation. n = number of myocardial segments; NS = not significantly different; *p <0.001 versus segments without abnormal Q waves.

wall motion (Figure 9). These results may indicate that the disappearance of abnormal Q waves in patients with Kawasaki disease does not necessarily mean the normalization of regional myocardial perfusion, metabolism or function, and also is not always related to metabolically active myocardial regions.

The present study also demonstrated that the persistence of abnormal Q waves on serial electrocardiograms was significantly shorter in metabolically active than in inactive segments (Table IV), suggesting that the early disappearance of abnormal Q waves may be more likely to imply the metabolic activity in the associated myocardial region, although a satisfactory explanation for this observation cannot be given at present.

The present study showed no significant difference in regional wall motion between tomographically ischemic but viable regions and PET scar regions (Figure 5). However, the previous study by Cohn et al[24] concerning the contractile reserve in ischemia has demonstrated myocardial "viability" on infusion of epinephrine or with post-extrasystolic potentiation. We measured only the resting wall motion and did not assess the contractile reserve. Therefore, the implication of the present study may be that regional wall motion at rest cannot reliably distinguish tomographically viable regions from scar regions.

There are several limitations in appreciating the results of the present study. Since we have not yet followed up the functional fate of the myocardial segments assessed in the present study, the term viable may not be exactly correct. The fasting FDG study may be limited by coexistence of the scar tissue and normal myocardium in group A segments. However, our recent study,[10] which was performed using the same methods as in the present study, demonstrated the reversibility of abnormal wall motion and perfusion after aortocoronary bypass surgery in about 80% of "group B" segments, but in only 20% of "group A" segments, suggesting that our methods can accurately predict the reversible ischemia.

We did not measure the plasma FDG concentration because of the difficulties in performing serial arterial blood sampling and sequential PET scans over 1 hour in children. Because the tracer uptake has been reported to depend on the tracer perfusate activity in the isolated working rat heart,[25] it might be necessary to know the plasma FDG concentration in assessing the tissue uptake of FDG. However, our preliminary study has indicated that percent FDG uptake (percent injected dose per 100 ml tissue) correlated well with the regional metabolic rate of glucose, as well as the fractional FDG uptake after correction of arterial plasma FDG concentration in the fasting state.[26] Therefore, percent FDG uptake appears to be a reliable index of regional myocardial glucose metabolism in the fasting condition.

The FDG study in the fasting state may also yield the problem of heterogeneity of FDG uptake within the same heart.[13] To avoid the distortion derived from this problem, we assessed the FDG uptake in each segment by comparing the patient's value with the normal value.

We did not study healthy children but healthy adult volunteers as control subjects. To perform PET scans in healthy children may not be feasible from the ethical aspect. Although glucose metabolic rates in children may differ from those in adults, the similar study conditions between patients and normal subjects, such as plasma substrate levels (Table II) and injected doses of radioactivity, may reduce this limitation.

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Usefulness of the Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio in Predicting Angiographic Coronary Artery Disease in Women

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To investigate the relation between lipids and angiographic coronary artery disease (CAD) in women, fasting lipid profiles were obtained on 108 women undergoing coronary angiography (group I). CAD, defined as ≥25% luminal diameter narrowing in a major coronary artery, was present in 57 (53%). Neither serum total cholesterol nor triglyceride levels correlated with the presence of CAD. Mean total/high-density lipoprotein (HDL) cholesterol ratio was higher among women with than without CAD (5.5 ± 0.3 vs 4.2 ± 0.2, $p < 0.0001$). Multiple regression analyses identified a higher total/HDL cholesterol ratio as the variable most predictive of the presence ($p < 0.001$), extent (number of narrowed arteries) ($p < 0.0001$), and severity (% maximum stenosis) ($p < 0.001$) of CAD. Age and lack of estrogen use were also independently associated with the presence of CAD, age and low-density lipoprotein cholesterol level were additional indicators of extent, and age was the only other discriminator of severity of CAD.

In 56 women with total cholesterol <200 mg/dl (group II), mean total/HDL cholesterol ratio was higher in women with (n = 24) than without CAD (4.3 ± 0.2 vs 3.5 ± 0.2, $p = 0.01$). Higher total/HDL cholesterol ratio was the variable most predictive of the presence of CAD ($p = 0.01$), and the lone variable associated with severity ($p < 0.001$) after adjustment for other risk factors. Age was independently associated with presence and extent, and hypertension was also independently related to extent. Thus, among these women, total/HDL cholesterol ratio is the best predictor of the presence, severity and extent of CAD in general, and is the best predictor of presence and severity in patients with total cholesterol <200 mg/dl.

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Lipids play a central role in atherogenesis[1] and coronary artery disease (CAD). Whereas CAD is the leading cause of death in women,[2] most epidemiologic and intervention studies examining the relation of lipids and CAD have excluded women from consideration.[3] Likewise, angiographic studies have not examined women as the principal subjects,[4] or have not determined a full lipid profile.[5] Thus, few studies have provided conclusive results regarding the relation of lipid values to CAD in women. Moreover, appropriate lipid intervention may be beneficial in women.[6] This study examines the relation between angiographically defined CAD and lipid levels in women undergoing elective diagnostic coronary angiography.

METHODS

Patient selection: The study group comprised 108 consecutive women (group I) undergoing elective, diagnostic coronary angiography at Georgetown University Hospital over an 8-month period and had a fasting lipid profile obtained the morning of the procedure. Patients with recent myocardial infarction (<6 weeks before angiography), unstable angina, prior coronary revascularization, or those taking lipid-lowering medications were excluded.

Of the 108 women in group I, 37 had a serum total cholesterol level <200 mg/dl. With use of the same exclusion criteria and the same method of data collection, 19 additional women with total cholesterol level <200 mg/dl were identified in a 6-month period preceding the initial study. Data from these patients were combined to form a group of 56 consecutive women with total cholesterol <200 mg/dl (group II).

Coronary arteriography: Selective coronary arteriograms were obtained using either the Judkins or Sones

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technique, and were independently reviewed by 2 cardiac radiologists without prior knowledge of the lipid values. Calipers were used to compare the diameter of a stenosed region with the nearest normal vessel diameter. Stenoses were then classified as a percent reduction of the original diameter.

CAD was considered to be present if at least 1 coronary artery system (left anterior descending, circumflex, right coronary artery) had a $\geq 25\%$ stenosis. Left main disease was not analyzed separately, as only 8 women had left main involvement. CAD was then classified by extent and severity. Extent was determined by the number of coronary arteries containing at least 1 stenosis of $\geq 25\%$ and was scored as number of vessels = 0, 1, 2 or 3. Severity was defined as the maximum percent stenosis found in any of the coronary artery systems of a given patient.

Lipid and lipoprotein measurements: As described previously,[4] total cholesterol and triglyceride levels were determined using enzymatic hydrolysis, and subsequent measurements were obtained spectrophotometrically using reagents from Boehringer Mannheim Diagnostics (Indianapolis, Indiana) and the Hitachi 737 (Tokyo, Japan) chemistry analyzer. Apolipoprotein B-containing lipoproteins were precipitated with phosphotungstic acid and magnesium chloride and subsequent centrifugation according to the manufacturer's specifications (Boehringer Mannheim Diagnostics). High-density lipoprotein (HDL) cholesterol measurement was then performed on the supernatant. Low-density lipoprotein (LDL) cholesterol was in turn calculated using a modified Friedewald formula[7]: $\text{LDL} = \text{total cholesterol} - (\text{HDL cholesterol} + \text{triglyceride} \times 0.16)$.

Risk factor assessment: Information on age, body mass index (kg/m^2), smoking, hypertension and diabetes mellitus, family history of CAD (documented CAD in a first-degree relative age <55 years in men and age <65 years in women), alcohol consumption (>1 drink/day), diet (adherence to a low fat, low cholesterol diet), exercise (>3 times weekly) and current use of medications (especially β blockers, diuretics and estrogens) that may influence serum lipid levels was obtained from the medical records and by direct questioning of the patients.

Data analysis: Patients were grouped into those with CAD absent or present. Differences between mean age, lipid and lipoprotein values between the groups were evaluated using Student's *t* test. Differences in categorical variables were measured using Fisher's exact test. A p value <0.05 was considered significant.

TABLE I Characteristics of Study Groups

	Group I (n = 108)		Group II (n = 56)	
Coronary Artery Disease	Absent (n = 51)	Present (n = 57)	Absent (n = 32)	Present (n = 24)
Demographics				
Age (years)	55 ± 2	62 ± 2†	57 ± 2	65 ± 2*
BMI (kg/m^2)	26.7 ± 1	26.5 ± 1	26.5 ± 1	24.8 ± 1
Cardiac risk factors (%)				
Diabetes mellitus	8	33†	6	25
Systemic hypertension	29	54*	25	54*
Cigarette smoking	18	21	13	21
Family history	25	28	25	50
Medications (%)				
β blocker	12	32*	9	33*
Diuretics	25	35	31	38
Estrogen	27	7†	25	8
Hygienic factors (%)				
Diet	31	35	38	25
Exercise	22	14	31	29
Alcohol use	24	11	28	25

*$p < 0.05$; †$p < 0.01$ versus coronary artery disease absent.

Age and body mass index are expressed as mean ± standard error of the mean. The other values are percentages of the patient subgroup.

BMI = body mass index.

Univariate Spearman correlation coefficients were computed for lipid values and age to characterize their relation to the extent and severity of CAD. Stepwise multiple logistic regression analysis was used to assess the contribution of each of the variables on the occurrence of CAD. Stepwise multiple linear regression analysis was used to evaluate the relative importance of several variables in contributing to the extent and severity of CAD.

RESULTS

Patient characteristics: Clinical data for patients in groups I and II, subdivided by the presence or absence of CAD, are listed in Table I. CAD was present in 53% of the women in group I. Women with CAD were significantly older, and the incidence of diabetes mellitus and hypertension was significantly higher in women with CAD. A significantly higher number of women with CAD were taking a β-blocking agent, whereas estrogen use was significantly higher among those without CAD. Women with or without CAD did not differ with other variables studied.

CAD was present in 43% of women in group II. Mean age was also significantly higher among women with CAD in this group. The incidence of hypertension, family history of CAD, and use of β-blocking agents was higher in those with CAD. Diabetes tended to be present in more patients with CAD, and more women without CAD tended to use estrogens, but these differences did not achieve statistical significance. Women with CAD absent or present did not differ with regard to any of the other risk factors listed.

Presence of coronary artery disease: In group I, mean levels of total cholesterol and triglycerides were not significantly different among patients with versus those without CAD (Table II). Mean levels of LDL cholesterol were significantly higher, and levels of HDL

TABLE II Lipid Values of Study Groups

Coronary Artery Disease	Group I		Group II	
	Absent	Present	Absent	Present
Total cholesterol (mg/dl)	213 ± 5	226 ± 7	180 ± 2	175 ± 5
LDL cholesterol (mg/dl)	133 ± 5	155 ± 6*	106 ± 3	107 ± 4
HDL cholesterol (mg/dl)	55 ± 3	46 ± 2	56 ± 3	48 ± 5
Triglycerides (mg/dl)	137 ± 11	155 ± 12	109 ± 8	129 ± 13
Total cholesterol HDL	4.2 ± 0.2	5.5 ± 0.3†	3.5 ± 0.2	4.3 ± 0.2*

Values are mean ± standard error of the mean.
*p < 0.01; †p < 0.0001 versus coronary artery disease absent.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

cholesterol lower in patients with CAD. Mean total/HDL cholesterol ratio was significantly higher in women with angiographic CAD.

In Group II, patients with or without CAD were also similar with regard to levels of total cholesterol and triglycerides, as well as LDL cholesterol levels. HDL cholesterol tended to be lower in those with CAD, but this difference was not significant. Of the lipid indices, only mean total/HDL cholesterol ratio differed significantly between patients with or without CAD, being higher in women with CAD.

Stepwise multiple logistic regression models were constructed using age, levels of total cholesterol, triglycerides, LDL and HDL cholesterol, total/HDL cholesterol ratio, and the presence of diabetes, hypertension, smoking history, β-blocker use and estrogen use as the independent variables to evaluate the effect of these factors on the occurrence of CAD in groups I and II. After adjustment for other risk factors, total/HDL cholesterol ratio was the most powerful independent variable related to the presence of CAD in both group I ($p <0.001$) and Group II ($p = 0.01$). In Group I, age ($p <0.01$) and lack of estrogen use ($p = 0.01$) also were independently correlated with the presence of CAD, whereas in Group II, age ($p <0.05$) was the only other variable selected after adjustment for other risk factors. Levels of total or LDL cholesterol and triglycerides were unrelated to the occurrence of CAD in either group.

Extent of coronary artery disease: On univariate analysis in group I, the extent of CAD correlated significantly with total/HDL cholesterol ratio ($r = 0.41$, $p = 0.00001$), LDL cholesterol level ($r = 0.33$, $p = 0.0006$), diabetes mellitus ($r = 0.30$, $p = 0.002$), low HDL cholesterol level ($r = -0.28$, $p = 0.003$), age ($r = 0.28$, $p = 0.004$), hypertension ($r = 0.23$, $p = 0.02$) and total cholesterol level ($r = 0.22$, $p = 0.02$).

In group II, extent correlated significantly with age ($r = 0.39$, $p = 0.002$), total/HDL cholesterol ratio ($r = 0.35$, $p = 0.008$), hypertension ($r = 0.31$, $p = 0.02$), and low HDL cholesterol level ($r = -0.28$, $p = 0.04$).

With stepwise multiple linear regression analyses, total/HDL cholesterol ratio ($p = 0.00004$), age ($p = 0.003$) and LDL cholesterol level ($p = 0.03$) were independently correlated with the extent of CAD in group I. In group II, extent was related to age ($p = 0.003$), smoking ($p = 0.005$) and hypertension ($p = 0.025$) and unrelated to any of the lipid parameters.

Severity of coronary artery disease: On univariate analysis in group I, the severity of CAD correlated significantly with total/HDL cholesterol ratio ($r = 0.44$, $p = 0.000002$), low HDL cholesterol level ($r = -0.32$, $p = 0.0007$), diabetes mellitus ($r = 0.30$, $p = 0.002$), LDL cholesterol level ($r = 0.27$, $p = 0.004$), age ($r = 0.27$, $p = 0.006$), hypertension ($r = 0.25$, $p = 0.008$) and lack of estrogen use ($r = -0.24$, $p = 0.01$).

In group II, severity correlated significantly with total/HDL cholesterol ratio ($r = 0.48$, $p = 0.0002$), diabetes mellitus ($r = 0.34$, $p = 0.01$), low HDL cholesterol level ($r = -0.32$, $p = 0.02$) and hypertension ($r = 0.26$, $p = 0.05$).

On stepwise multiple logistic regression analysis, total/HDL cholesterol ratio ($p = 0.0001$) and age ($p = 0.0004$) were significantly correlated with severity in group I. In group II, total/HDL cholesterol ratio ($p = 0.0002$) was the lone variable independently associated with severity.

DISCUSSION

The results of this study indicate that among women undergoing diagnostic coronary angiography for suspected CAD, total/HDL cholesterol ratio is the lipid parameter most predictive of the presence, severity and extent of CAD after adjustment for other risk factors (group I), and most predictive of presence and severity in women with total cholesterol level <200 mg/dl. Furthermore, on multiple regression analyses, age was independently associated with the presence, extent and severity of CAD in group I and presence and extent in group II. None of the other variables was independently related to severity in either group. Lack of estrogen use was independently associated with presence of CAD. LDL cholesterol was independently associated with extent of CAD in group I, and hypertension was the only other variable associated with extent in group II. Total cholesterol and triglyceride levels did not distinguish between patients with versus those without CAD in either group.

Our previous work[4] and other epidemiologic and angiographic studies have also shown that total/HDL cholesterol ratio is a reliable discriminator of the presence of CAD in women, regardless of the level of total cholesterol.[8,9] The ratios of 4.5 to 5.0 seem to be dichotomous, in agreement with our finding. Furthermore, the ratio was a significant discriminator of the presence, severity and extent of CAD in women in a previous angiographic study.[10] Recently, Miller et al[11] showed that the ratio is significantly higher among women with total cholesterol <200 mg/dl, the ratio is significantly higher in women with than without CAD. Thus, despite different study designs and definitions of CAD, total/HDL cholesterol ratio emerges as the most powerful lipid parameter predictive of CAD in women. On the other hand, the Framingham Study suggested that levels of HDL cholesterol and triglycerides are important predictors of CAD, especially in elderly women.[8,12] This discrepancy is possibly due to the fact that the Framingham Study was an epidemiologic study without angiographic demonstration of CAD. The Coronary Artery Surgery Study Registry showed that clinical definition of CAD in women may not be as reliable, because only 50% of women with a clinical diagnosis of angina had angiographic CAD.[13]

Our definition of CAD merits explanation. Recent studies have suggested that the initial angiographic severity of coronary stenoses does not predict the time or the location of subsequent coronary occlusion,[14] and that plaques producing only mild to moderate angiographic luminal stenosis comprise the majority of those undergoing abrupt rupture, resulting in acute ischemic syndromes.[15] Coronary vasomotor studies have shown that even angiographically normal-appearing coronary segments in patients with CAD may have diffuse endothelial dysfunction, indicating early atherosclerosis that is not yet detectable by angiography.[16] Thus, we chose our definition of CAD as ≥25% luminal diameter narrowing in order to identify patients with early, but not necessarily clinically significant atherosclerosis.

Postulated mechanisms: Previous studies in women have shown that total/HDL cholesterol ratio is a significant predictor of CAD; thus, it is unlikely that our result is a chance finding. Other angiographic studies have not found the ratio to be predictive, either because the ratio was not measured,[17] or because the number of patients may have been too small.[18] A possible explanation for our result is that we chose 25% luminal diameter narrowing as the presence of CAD and the ratio may be the best predictor of early CAD. Furthermore, the increasing ratios with the presence of CAD may reflect the lipid changes that occur with aging. The Framingham Study[19] showed that LDL cholesterol and triglycerides, and thus total cholesterol levels increase with aging, whereas levels of HDL cholesterol stay relatively constant. This trend would result in increasing total/HDL cholesterol ratios with aging. This hypothesis is supported by the fact that age is an independent predictor of CAD. Alternatively, the increasing ratio may reflect the additive effect of varying cardiac risk factors; HDL cholesterol level can be adversely affected by diabetes, cigarette smoking and other hygienic factors,[20] and with the presence of more risk factors, the likelihood of CAD increases.[17]

Need for detecting early coronary artery disease in women: Although CAD occurs about a decade later in women than in men,[21] and is uncommon in premenopausal women, women with overt CAD have a worse prognosis than men. Women, especially black women who experience a myocardial infarction, have increased morbidity and mortality than men.[3,22] Women undergoing coronary artery bypass grafting tend to have a higher rate of incomplete revascularization, reduced graft patency rate, less symptomatic relief[23] and higher operative mortality[24] when compared with men. Similarly, percutaneous transluminal coronary angioplasty tends to be less successful in women.[25] Recent regression studies would suggest that it is possible to reverse the atherosclerotic process.[26] Thus, it is essential to identify women at risk of CAD who might benefit from efforts to alter their risk factors.

Study limitations: As with other studies, black women comprised a relatively small percentage (26%) of the subjects in the present study. However, previous reports have similarly identified total/HDL cholesterol ratio as the most predictive indicator of CAD among black women.[27] Only 1 set of lipid measurements was obtained from each patient, although recent studies suggest that there can be significant day-to-day variability of serum lipid levels[28] and wide within-person fluctuations.[29] Because our patients were preselected for coronary angiography, they are neither a representative sample of women in the general population, nor that of women with CAD.

Future studies: Major lipid intervention studies have generally excluded women from consideration; thus, the benefits of altering lipid values and the subsequent rate of coronary events have not been established in women. Such a study with women as the principal participants needs to be performed to address whether lipid intervention is beneficial in women. Moreover, the relation between lipid values and CAD in black women has not been well established, despite the fact that black women may have a poorer prognosis after a coronary event than their Caucasian counterparts.[22]

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Radiofrequency Catheter Ablation of Accessory Pathways: A Learning Experience

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Success rates of approximately 90% have recently been reported with radiofrequency catheter ablation of accessory pathways. This study determined whether this success could be repeated using a conservative approach generally limiting fluoroscopy time to 1 hour. Consecutive patients referred for management of arrhythmias associated with accessory atrioventricular pathways were included over a 9-month period. Ablation was attempted in 75 patients with 84 pathways. Overall success rate (including second attempts in 9 patients) was 60 of 84 accessory pathways (71%). Success rates for the first 3 months (n = 23) were 52%, the second 3 months (n = 23) 60% and the last 3 months (n = 38) 90%. Success rate varied with pathway location, with left lateral pathways having the best early success rates. Mean fluoroscopy time for successful procedures of 33 ± 21 minutes was shorter than the time for unsuccessful procedures of 63 ± 24 minutes (p = 0.001). There were no major complications and no patients with successful procedures (n = 53) have had recurrence of accessory pathway conduction or reciprocating tachycardia (follow-up 1 to 10 months). A conservative approach can yield success rates approaching 90% in a short time. The absence of major complications supports earlier reports suggesting that radiofrequency catheter ablation of accessory pathways is a reasonable first-line therapy in the Wolff-Parkinson-White syndrome.

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Traditional management of Wolff-Parkinson-White syndrome is pharmacologic with operative therapy indicated when drug therapy is not satisfactory. Recent reports describe a new technique that involves positioning a catheter at the site of the accessory pathway and ablating it with radiofrequency energy.[1-4] The remarkable success with this technique has led to the suggestion that ablation be a primary therapy in the Wolff-Parkinson-White syndrome.[1] However, it is still unclear to what extent these results are reproducible or to what extent they are a reflection of outstanding commitment by dedicated persons. We describe our initial experience using catheter ablation as first-line therapy in a consecutive series of patients with accessory atrioventricular pathways.

METHODS

Patients: Seventy-five consecutive patients were referred for evaluation and treatment of Wolff-Parkinson-White syndrome. Ablation was attempted in all patients unless findings did not warrant ablation or if patients were referred expressly for operative or pharmacologic therapy. All patients provided written and verbal informed consent.

Diagnostic study: The diagnostic techniques and criteria used in our laboratory have been described.[5] Electrode catheters were positioned in each of the high right atrium, His bundle regions and right ventricular apex through the right femoral vein. A multipolar catheter was positioned in the coronary sinus by way of the left subclavian vein. Programmed stimulation consisted of incremental atrial and ventricular pacing to block and extrastimulus testing using at least single extrastimuli at 2 cycle lengths. The goals of the study were to demonstrate the participation of the accessory pathway in patients' arrhythmias and to localize accessory pathways. Programmed electrical stimulation was repeated after ablation.

Catheter ablation: Patients were sedated with midazolam and fentanyl. A 5,000 U bolus of heparin was given when catheters were positioned in the left atrium or left ventricle. Ablation immediately followed the diagnostic study. A 7Fr quadripolar deflectable catheter (Mansfield-Webster, Watertown, Massachusetts) with a 4 mm tip was used. The atrial ventricular region was mapped in the area of interest looking for electrograms

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with both atrial and ventricular potentials ("ring" electrogram) (Figure 1). Optimal position consisted of sites showing earliest ventricular activation during anterograde preexcitation or earliest atrial activation during retrograde preexcitation, or both. The bipolar electrogram between the distal and the second electrode (filtered at 40 to 400 Hz) and the unipolar electrogram from the distal tip (filtered at 0.50 to 400 Hz) were recorded with 5 surface leads and selected intracardiac leads. Orientation to the atrioventricular ring was facilitated by the standard catheters positioned at the His bundle and coronary sinus.

One or more of the following criteria determined the site of anterograde preexcitation: (1) the presence of atrial and ventricular electrograms on the same recording, each with a rapid intrinsic deflection; (2) the presence of an electrogram compatible with an accessory pathway potential between the atrial and ventricular electrograms or the presence of continuous electrical activity between the atrial and ventricular electrograms, possibly representing accessory pathway activation; (3) the recording of the intrinsic deflection of the ventricular electrogram preceding the onset of the delta wave on the surface electrocardiogram; and (4) a QS pattern on the unipolar ventricular electrogram with the rapid intrinsic deflection preceding the onset of the delta wave.

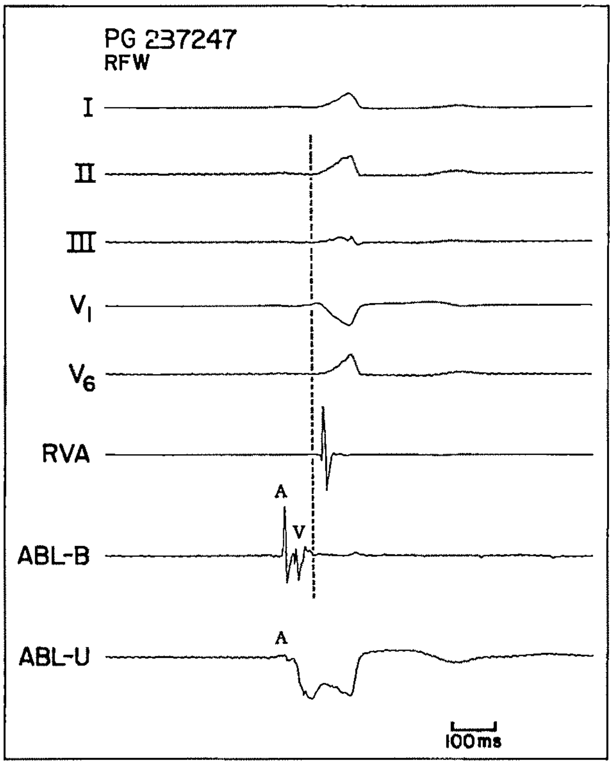

FIGURE 1. Recordings before ablation in a patient with a right free wall pathway. Atrial (A) and ventricular (V) potentials on the ablation catheters (ABL) recording both have rapid intrinsic deflections indicating proximity to the tricuspid valve anulus. The ablation catheter tip is close to the accessory pathway since the ventricular potential precedes the onset of the delta waves on the electrocardiogram. A fast initial negative deflection on the ventricular component of the unipolar electrogram also indicates proximity to the onset of ventricular activation. ABL-B = ablation catheter bipolar recording; ABL-U = ablation catheter unipolar recording; leads I, II, III, V_1 and V_6 = surface electrocardiogram.

One or more of the following criteria were used for determining the site of retrograde preexcitation during reciprocating tachycardia: (1) the presence of a "ring electrogram" as previously defined; (2) the presence of an accessory pathway potential between the ventricular and atrial electrograms; and (3) the site of earliest recorded retrograde atrial activation during tachycardia.

Left lateral accessory pathways: Mapping was attempted from the ventricular side of the anulus in all cases. The ablation catheter was advanced from the femoral artery in retrograde manner across the aortic valve and moved under the mitral valve between the leaflet and the endocardial surface of the posterior and lateral left ventricular wall. Adequate position was obtained when the ablation catheter tip moved synchronously with the adjacent coronary sinus catheter. When acceptable positions could not be obtained from the ventricular side, the mitral valve anulus was mapped from the atrial side. A transeptal approach was used to map the atrial aspect of the mitral valve anulus in 3 cases.

Other accessory pathways: For right-sided accessory pathways, mapping of the tricuspid valve anulus was performed through the right femoral vein. If difficulty was encountered, catheter manipulation was done from the left subclavian vein. For posteroseptal accessory pathways, early atrial or ventricular potentials were sought around the coronary sinus ostium. When the earliest potentials were >10 mm within the coronary sinus, mapping was done from the left ventricle as described.

Energy source: Radiofrequency current (400 to 600 mA) was applied between the 4 mm tip electrode of the ablation catheter and a back plate. Initially, an electrosurgery unit (Valley Lab, Boulder, Colorado) delivering a 500 kHz continuous wave was used with coagulation energy. An ammeter allowed real-time assessment of current flow. The last 15 cases were done using a Radionics RFG-3C radiofrequency lesion generator (Radionics Inc., Burlington, Massachusetts), which allowed simultaneous measurement of current, voltage, power and impedance. For the last 4 months a filter that allowed observation of surface and intracardiac electrograms during radiofrequency current delivery (Bloom Associates, Reading, Pennsylvania) facilitated real-time assessment of the loss of preexcitation (Figure

TABLE I Clinical Characteristics of Patients

	Pts. (n = 75)	%
Accessory pathways	84	—
1	67	89
2	7	9
3	1	1
Retrograde-only conduction	9	11
Accessory pathway location		
Left lateral	57	68
Posteroseptal	16	19
Right free wall	9	10
Anteroseptal	2	2

TABLE II Results of Radiofrequency Accessory Pathway Ablation

	No. of Patients (total)	Success	% Success	No. of Accessory Pathways (total)	Success	% Success
	75	53	71	84	60	71
All Accessory Pathway Locations						
Group I	20	11	55	23	12	52
Group II	22	13	59	23	14	60
Group III	33	29	88	38	34	90
All Groups*						
LL	53	42	79	57	45	79
PS	15	7	47	16	8	50
RFW	8	4	47	16	8	56
RAS	2	2	100	2	2	100

*Three patients had 2 accessory pathways in different regions.

Group I = September to November; Group II = December to February; Group III = March to May; LL = left lateral; PS = posteroseptal; RAS = right anteroseptal; RFW = right free wall.

2). Current was generally discontinued if a therapeutic effect was not observed within 5 to 10 seconds or with an increase in impedance.

Variables assessed and data analysis: End points assessed were success rates, fluoroscopy time and total number of radiofrequency applications. Success was defined as a loss of accessory pathway conduction that persisted for >30 minutes in the electrophysiology laboratory with no late return of preexcitation or tachycardia. An obtunded accessory pathway was one in which pathway conduction was temporarily lost or the accessory pathway refractory period or block cycle length was prolonged by >50 ms. To assess the effects that experience had on success rates, results were analyzed in 3-month intervals from September 1990 to May 1991. Continuous variables were expressed as mean ± standard deviation. Procedural variables were compared using Student's *t* test for unpaired data. A p value <0.05 was considered significant.

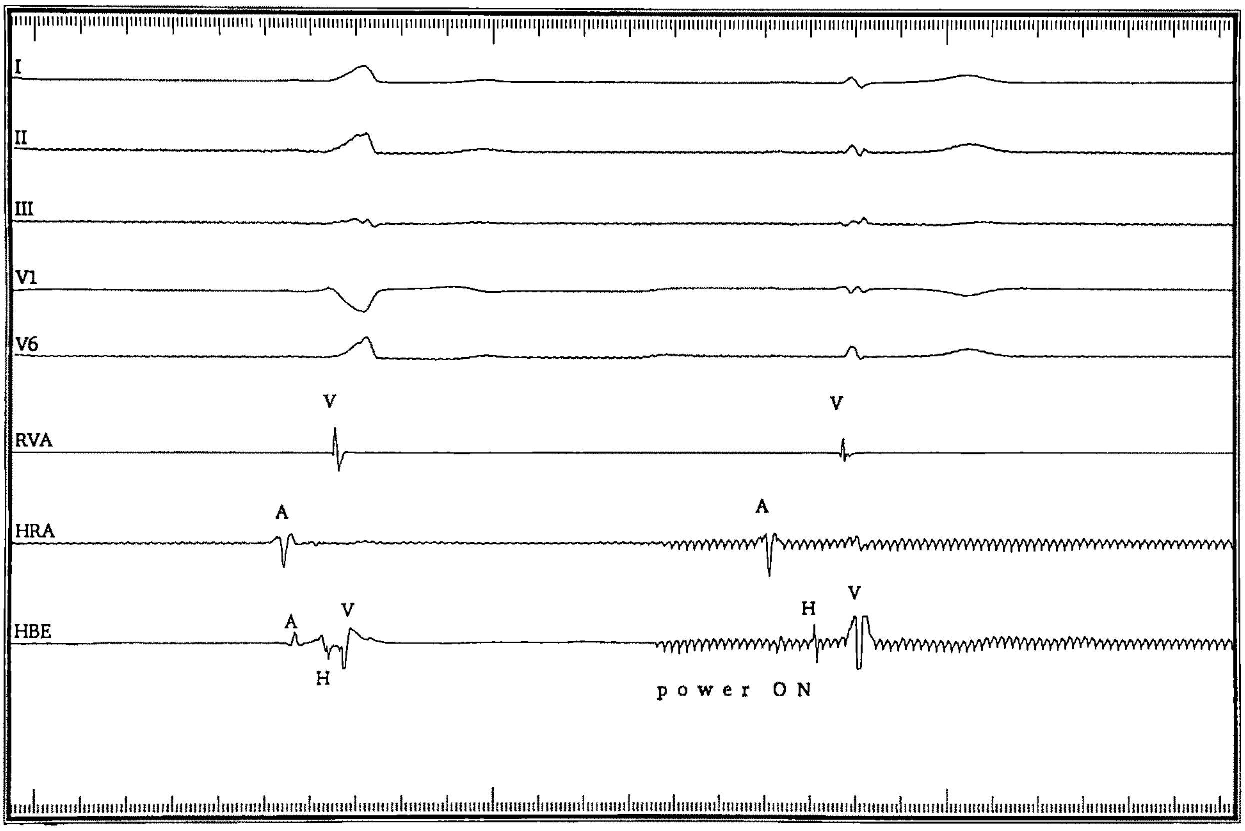

FIGURE 2. Records during ablation of patient in Figure 1. The electrograms at the ablation site (Figure 1) are not recorded during current delivery. Onset of current is indicated by the artefact noted on the intracardiac records. Accessory pathway conduction is lost within 1 cycle. H = His; HBE = His bundle electrogram; HRA = high right atrium; other abbreviations as in Figure 1.

TABLE III Group Success Rates for Radiofrequency Accessory Pathway Ablation by Accessory Pathway Location

	Group I		Group II		Group III		Total	
AP Location	n	(%)	n	(%)	n	(%)	n	(%)
LL	10/15	67	10/14	71	25/28	89	44/57	77
PS	2/7	29	2/4	50	4/5	80	8/16	50
RFW	0/1	0	1/4	25	4/4	100	5/9	56
RAS	—	—	1/1	100	1/1	100	2/2	100

AP = accessory pathway; n = number of accessory pathways ablated/number of accessory pathways attempted; other abbreviations as in Table II.

RESULTS

Patients and pathways: Ablation was attempted in 75 patients (55 men) with 84 accessory pathways. The median age was 26 years (range 8 to 67). All had recurrent supraventricular tachycardia or atrial fibrillation with rapid ventricular rates (Table I).

Fifty-five of 84 accessory pathways were ablated on the initial attempt for a success rate of 66%. Nine patients underwent a second attempt and this succeeded in 5 (3 left lateral and 2 posteroseptal accessory pathways). Therefore, overall success was 60 of 84 accessory pathways (71%) or 53 of 75 patients (71%). Success rates varied with location of the accessory pathway (Table II).

Clinical experience with time: Results were examined for 3 consecutive intervals. The groups included patients in whom ablation was attempted from September to November 1990 (group I), December 1990 to February 1991 (group II) and March to May 1991 (group III).

For the 20 group I patients, overall success rate for the 23 accessory pathways was 52% (12 of 23). Twenty-two patients with 23 accessory pathways underwent ablation attempts between December 1990 and February 1991 (group II), with an overall success rate of 60% (14 of 23). In the final 3 months (group III), ablation was attempted in 33 patients with 38 accessory pathways, with an overall success rate of 90% (34 of 38) (Table III).

Fluoroscopy time included the time taken for the diagnostic procedure and the time spent mapping and ablating. This was not systematically documented during the first 3 months but generally did not exceed 60 minutes. Fluoroscopy time was therefore assessed for only group II and III patients. Mean time for successful ablation for all accessory pathway ablations was 33 ± 21 minutes (range 6 to 88). As expected, mean fluoroscopy time was longer for unsuccessful procedures at 63 ± 24 minutes (range 20 to 91) ($p = 0.001$).

Number of ablation attempts: The number of radiofrequency applications for successful ablation was markedly different than the number for unsuccessful ablation. Mean number of attempts for group I patients in whom ablation was successful was 4.8 ± 3.9 (range 1 to 14). For group II patients the mean was 5.4 ± 4.2 (range 1 to 18) and for group III patients it was 6.2 ± 5.0 (range 1 to 20). Mean number of attempts for all groups with unsuccessful ablations was higher (14.4 ± 9.5 vs 5.7 ± 4.6, $p < 0.0001$). The maximum number of attempts was 32, with 9 of 27 patients with failed accessory pathway ablation having >20 attempts.

Myocardial damage and complications: Creatinine kinase-MB fractions were determined immediately and every 8 hours for 24 hours after ablation. The upper level of normal in our laboratory is 10 U/liter. Mean peak of 7.9 ± 6.5 U/liter for 41 patients with successful ablations was slightly <11.4 ± 9.3 U/liter for 21 patients with unsuccessful ablations ($p = 0.08$). All patients were observed in the arrhythmia monitoring unit for 48 hours. Pneumothorax related to subclavian vein puncture ($n = 1$), incomplete perforation of the left atrial appendage noted incidentally at elective surgery ($n = 1$), atrial fibrillation during radiofrequency current delivery ($n = 2$) and ventricular fibrillation with an abrupt increase in impedance ($n = 2$) were noted.

Follow-up: Fifty-three patients had successful procedures as assessed by clinical and electrocardiographic follow-up ($n = 43$) or by repeat electrophysiologic study at 3 months ($n = 10$). Twenty-two patients had unsuccessful procedures. Of these 22 patients, 15 underwent operative ablation (left lateral 7, posteroseptal 6, right free wall 2). In 10 patients the accessory pathway was either lost temporarily or conduction was severely impaired (obtunded). Two patients underwent surgery, and 3 asymptomatic patients returned for testing at 3 months and had no accessory pathway conduction. Three patients have had spontaneous reciprocating tachycardia, of whom 2 have undergone successful ablation on a second study and 1 awaits repeat catheter ablation. Two patients had inducible reciprocating tachycardia but no spontaneous recurrence.

DISCUSSION

With the recent emergence of catheter ablation for the treatment of symptomatic Wolff-Parkinson-White syndrome,[6] an increasing number of centers are beginning an ablation program. Because of fears about radiation exposure and complications with catheter manipulation and current delivery in the ventricles, there are concerns about the safety of the procedure relative to time-proven therapies such as surgical ablation. In experienced centers, operative ablative therapy is virtually 100% successful with little mortality or morbidity.[7,8] Our approach as we began ablating accessory pathways was to integrate ablation with the surgical program and avoid excessively prolonged ablation procedures during our learning phase. Fluoroscopy time was limited to 60 minutes unless circumstances compelled us to continue for a brief time longer. Our initial success rate of 52% reflected this conservative approach. During the latter part of our 9-month series, success rates approached 90%.

Improvement in success over time was noted for left lateral, posteroseptal and right free wall accessory pathways. The learning curve for lateral accessory pathways was steeper than for other pathway locations. This reflected the usually greater ease in mapping along the mitral valve anulus compared with mapping the atrial side of the tricuspid valve anulus. Improvements in identification of optimal electrograms on the ablation catheter recordings also contributed to success.[9] Finally, success was also importantly related to acquiring optimal equipment to deliver and monitor ongoing ablation. The acquisition of filters that allowed clear observation of the surface and intracardiac electrograms during radiofrequency application was a key technical improvement.

Complications during and after the procedure were few and were primarily arrhythmic. Acute atrial and ventricular fibrillation have not been previously emphasized and were likely due to direct electrical effects as impedance rapidly increased. The development of devices that monitor tip temperature and impedance and automatically discontinue current should eliminate this complication.[10] Other previously reported serious complications were not observed.[1,2] Although not prospectively evaluated, there was no evidence for impairment of left ventricular function. It has been previously shown that radiofrequency current delivered at energy levels and durations similar to those used by us result in small, discrete lesions.[3,10,11] The very minimal myocardial damage was reflected in the small increase seen in the creatinine kinase level.

These data support the suggestion of others that radiofrequency catheter ablation is reasonable first-line therapy in Wolff-Parkinson-White syndrome. A conservative approach, limiting fluoroscopy time in most cases to 60 minutes, will yield success rates approaching 90% in a relatively short time.

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Reduction in Medical Care Cost Associated with Radiofrequency Catheter Ablation of Accessory Pathways

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The cost of definitive therapy was compared in 25 patients who underwent radiofrequency catheter ablation of accessory pathways in 1990 and 25 patients who underwent surgical ablation of accessory pathways in 1989. In the radiofrequency group, 23 of 25 patients had a single accessory pathway and the remaining 2 patients each had 2 accessory pathways. In the surgical group, 20 patients had a single accessory pathway and 5 patients each had 2 accessory pathways. The success rate was 96% in each group. The mean duration of hospitalization was 3 ± 1 days in the radiofrequency group and 9 ± 4 days in the surgical group ($p < 0.0001$). All the cost data are expressed in fiscal year 1990/1991 dollar values. The total cost of therapy in the radiofrequency group was $14,919 ± $6,740 compared with $53,265 ± $12,755 in the surgical group ($p < 0.0001$). The cost of radiofrequency ablation consisted of a hospital charge of $7,753 ± $3,472 and physician fees of $7,166 ± $3,439. The hospital charge included charges for use of the electrophysiology laboratory, hospital stay, electrocardiograms, echocardiograms and blood studies. The cost of surgery consisted of a hospital charge of $37,708 ± $10,179 and physician fees of $15,557 ± $3,149. The hospital charge in the surgical group included the costs of a baseline electrophysiology study, in-hospital care and a follow-up office visit. In conclusion, radiofrequency catheter ablation of accessory pathways results in a dramatic reduction in the cost of definitive therapy in patients with the Wolff-Parkinson-White syndrome.

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Radiofrequency catheter ablation has been shown to be a safe and efficacious means of interrupting accessory pathway conduction.[1,2] This treatment method has a high degree of patient acceptance because it eliminates the need for open-chest surgery. An important additional advantage of this therapy is the anticipated cost-savings associated with its use, but few data on this aspect have been published to date. Therefore, this study describes the cost of accessory pathway ablation using radiofrequency current and compares this cost with that of a standard surgical approach.[3]

METHODS

This was a retrospective study of 25 consecutive patients who underwent surgical ablation of accessory pathways in 1989 and 25 consecutive patients who underwent radiofrequency ablation of accessory pathways in 1990. All the patients in the study were referred to the University of Michigan Medical Center for management of recurrent supraventricular tachyarrhythmias.

Electrophysiologic study: All patients underwent a diagnostic electrophysiologic test at least 5 half-lives after discontinuation of all antiarrhythmic drugs and after providing informed consent. Three 6Fr quadripolar catheters were inserted into a femoral vein and positioned at the high right atrium, across the tricuspid valve to record the His bundle electrogram and against the right ventricular apex or septum. An additional quadripolar catheter was inserted into the subclavian or internal jugular vein and positioned in the coronary sinus. After the catheters were in place, 3,000 U of heparin were administered intravenously. Programmed atrial and ventricular stimulation was performed using a Bloom DTU 201 stimulator (Bloom Associates, Narbeth, Pennsylvania). Standard techniques were used to elucidate the presence of an accessory pathway and to confirm its participation as a critical limb of the tachycardia circuit.[4] A Siemens-Elema Mingograf 7 ink-jet recorder provided both a continuous oscilloscopic display and a permanent record of leads V_1, I and III and the intracardiac electrograms.

Radiofrequency ablation group: The group comprised 11 men and 14 women (mean age 40 ± 16

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years, range 14 to 74). Mean duration of symptoms was 21 ± 17 years (range of 1 month to 60 years). They had been treated with a mean of 2 ± 1 antiarrhythmic drugs before undergoing radiofrequency ablation and most of these drugs had been poorly tolerated or were ineffective. Twenty-three of the 25 patients had a single accessory pathway and the remaining 2 patients each had 2 accessory pathways. Fifteen of the accessory pathways were left-sided, 9 were septal and 3 were right-sided; 17 displayed manifest preexcitation and 10 were concealed.

On completion of the diagnostic portion of the electrophysiologic study, radiofrequency catheter ablation was attempted during the same session. The ablation protocol was approved by the Human Research Committee at the University of Michigan and all patients provided written informed consent before undergoing the procedure. Radiofrequency ablation was performed using a 7Fr quadripolar deflectable tip catheter with a 4 mm distal electrode and 5 mm interelectrode spacing (Mansfield, Watertown, Massachusetts). For left-sided accessory pathways, the catheter was advanced from the femoral artery to the left ventricle and positioned in the atrioventricular sulcus under the mitral valve anulus. For right-sided accessory pathways, the catheter was advanced from the inferior cava to the right atrium at the level of the tricuspid valve. For septal accessory pathways, the ablation catheter was advanced from the superior or inferior vena cava to the coronary sinus os or the anterior atrial septum. A detailed description of the mapping and ablation technique has been previously provided.[2]

On completion of the radiofrequency ablation procedure, the patients were admitted to a telemetry unit for 48 hours of monitoring. Three serial blood samples were obtained at 8-hour intervals for determination of the plasma concentrations of creatine kinase and its MB subfraction. A daily 12-lead electrocardiogram was recorded and cross-sectional echocardiography and Doppler study were performed within 24 hours of the radiofrequency ablation. In patients in whom the accessory pathway was concealed, a brief electrophysiologic test was performed after 48 hours to confirm successful ablation. In patients in whom the accessory pathway was manifest, the absence of delta waves on the 48-hour electrocardiogram was regarded as evidence of a successful outcome and a repeat electrophysiologic study was not performed before discharge from the hospital. All patients underwent a final electrophysiologic test after 3 months on an outpatient basis to assess the long-term efficacy of the procedure.

Surgical group: This group comprised 14 men and 11 women (mean age 30 ± 11 years, range 13 to 60). The mean duration of symptoms was 11 ± 11 years (range 1 month to 40 years). The patients had been treated with 2 ± 2 antiarrhythmic drugs before undergoing surgery. These drugs had been ineffective or associated with unacceptable side effects for almost all of the patients. Twenty of the 25 patients had a single accessory pathway and the remaining 5 patients each had 2 accessory pathways. Twenty of the accessory pathways were left-sided, 8 were septal and 2 were right-sided; 20 displayed manifest preexcitation and 10 were concealed.

Surgical ablation was performed using an endocardial approach.[3] After the induction of general anesthesia, the chest was opened through a median sternotomy incision. The accessory pathway(s) was localized using standard mapping techniques[4] and the patient was then placed on cardiopulmonary bypass. When the surgical ablation was completed the patient was weaned from cardiopulmonary bypass and intraoperative epicardial mapping was repeated to evaluate the efficacy of the surgical dissection. Before discharge from the hospital, bedside pacing using temporary epicardial pacing leads was performed to confirm a successful surgical result.

Cost analysis: Retrospective review of each patient's clinical record was performed to determine the number, duration and dates of hospital admissions and the number and dates of office visits that were related directly to the ablation procedure. Only charges billed from the University of Michigan Medical Center were included in the present analysis. The costs incurred by each patient were divided into hospital and physician charges. Itemized bills were obtained from the patients' accounts office for all ablation-related admissions and office visits. The hospital costs include the charges for room and board, operating room or electrophysiology laboratory charges, and charges for nursing and ancillary care, drugs, blood tests, x-rays, electrocardiograms and echocardiograms. The analysis incorporated the cost of a 1-month follow-up office visit and an electrocardiogram at rest for all patients. All patients treated surgically had a chest x-ray during the follow-up office visit and this cost was also included.

Physician charges for all ablation-related hospital admissions and office visits were obtained from the relevant physician-associates groups at the University of Michigan Medical Center. The cost of the 3-month follow-up electrophysiologic study in the radiofrequency ablation group was excluded from the present analysis because the indication for this study was based on the investigational nature of the procedure and the need to document accurately its long-term effects. As radiofrequency ablation becomes established in clinical practice, this follow-up study will not be necessary.

To conduct a valid comparison and to provide cost data that are meaningful in 1991, an adjustment was made to convert all costs to their 1990/1991 fiscal year dollar values. The annual increase in hospital charges

TABLE I Age, Number of Accessory Pathways, Duration of Hospital Stay and Individual Costs in 25 Patients Undergoing Surgical Ablation

Pt. No.	Age (yr)	No. of APs	Hospital Stay (days)	Hospital Charges ($)	Physician Charges ($)	Total Charges ($)
1	38	1	10	35,437	16,280	51,717
2	23	1	6	30,815	14,585	45,400
3	42	1	7	28,668	15,308	43,976
4	60	1	8	34,977	16,898	51,875
5	39	1	8	33,931	10,937	44,868
6	15	1	8	33,470	15,945	49,415
7	28	1	13	41,163	17,586	58,749
8	28	2	11	36,053	15,774	51,827
9	28	1	8	32,441	15,616	48,057
10	29	2	10	45,218	15,633	60,851
11	30	2	6	33,590	14,574	48,164
12	47	1	10	46,893	17,647	64,540
13	23	1	6	33,781	14,681	48,462
14	28	1	15	36,068	10,319	46,387
15	22	1	6	30,031	15,286	45,317
16	15	1	7	28,945	15,178	44,123
17	41	2	11	62,111	22,625	84,736
18	33	1	8	38,324	14,443	52,767
19	22	1	10	33,839	13,931	47,770
20	20	2	24	72,636	24,892	97,528
21	41	1	11	35,659	9,832	45,491
22	36	1	8	40,844	15,099	55,943
23	17	1	12	37,203	15,685	52,888
24	23	1	7	28,892	14,477	43,369
25	13	1	8	31,714	15,700	47,414
Mean ± SD	30 ± 11		9 ± 4	37,708 ± 10,179	15,557 ± 3,149	53,265 ± 12,755

APs = accessory pathways; SD = standard deviation.

and physician fees was obtained from the University of Michigan Medical Center budget and medical service plan offices respectively. The annual increase in hospital charges was 7.4% for fiscal year 1989/1990 and 13.1% for fiscal year 1990/1991. The annual increase in physician fees was 7.36% for fiscal year 1989/1990 and 5.7% for fiscal year 1990/1991. The annual physician fee increase is based on the Physicians Services Index of the Consumer Price Index using the 3-month period of February through April. The dollar values presented in this study represent the mean total of what was billed to each patient for either radiofrequency or surgical ablation. The cost to charge ratio expresses the actual cost of delivering a service as a proportion of what is billed to the patient for providing that service. In the present study, the cost-to-charge ratio for hospital services was 0.56 in the radiofrequency group and 0.61 in the surgical group. Cost-to-charge ratios are not available for professional fees.

Statistical analysis: The costs of radiofrequency and surgical ablation were compared using the unpaired *t* test. A p value <0.05 was considered significant and all numerical data are expressed as mean ± standard deviation.

RESULTS

Patient characteristics: The patients in the radiofrequency group were significantly older than the patients in the surgical group (40 ± 16 vs 30 ± 11 years; p <0.01). The duration of arrhythmia symptoms before ablation was significantly longer in the radiofrequency group than in the surgical group (21 ± 17 vs 11 ± 11 years; p <0.05). There was no significant difference in the mean number of antiarrhythmic drugs used to treat patients before they underwent ablation (1.9 ± 1.4 in the radiofrequency group versus 2.4 ± 1.6 in the surgical group).

Efficacy of ablation: Radiofrequency ablation was achieved successfully in 22 of 25 patients (88%) during a single hospital admission and in 2 of 25 patients (8%) during 2 hospital admissions. Surgery was successful for 24 of 25 patients (96%) and 21 of 25 patients had a single hospital admission. Among the 4 patients who had >1 hospital admission, 3 patients required 2 hospital admissions and 1 patient had 3 hospital admissions. This latter patient (no. 12, Table I) was referred for management of refractory supraventricular tachycardia and had a 1-day hospital admission for a baseline electrophysiologic study and stabilization on a medical regimen pending surgery. He had a 7-day admission for surgical ablation of a concealed left-sided accessory pathway and a 2-day readmission 9 days after discharge from the hospital for management of atrial fibrillation.

Cost data (Tables I and II): The mean total cost of definitive therapy in the radiofrequency group was $14,919 ± $6,740 compared with $53,265 ± $12,755 in the surgical group (p <0.0001). Analysis of the

TABLE II Age, Number of Accessory Pathways, Duration of Hospital Stay and Individual Costs in 25 Patients Undergoing Radiofrequency Ablation

Pt. No.	Age (yr)	No. of APs	Hospital Stay (days)	Hospital Charges ($)	Physician Charges ($)	Total Charges ($)
1	25	1	2	4,961	4,440	9,401
2	31	1	4	9,231	8,380	17,611
3	38	1	2	5,317	4,702	10,019
4	50	1	5	7,502	4,974	12,476
5	31	1	2	2,597	5,351	7,948
6	40	1	5	7,502	5,243	12,736
7	35	1	4	8,997	7,181	16,178
8	14	2	5	15,149	16,537	31,686
9	50	1	2	6,982	9,491	16,473
10	24	1	2	7,212	8,904	16,116
11	42	1	2	4,756	5,160	9,916
12	57	1	4	9,174	8,711	17,885
13	32	1	5	16,592	15,387	31,979
14	42	1	3	6,784	4,203	10,987
15	29	1	2	5,313	4,393	9,706
16	54	1	2	5,619	5,018	10,637
17	37	1	2	4,855	4,767	9,622
18	16	1	2	4,984	4,242	9,226
19	63	1	5	12,453	9,335	21,788
20	60	2	4	13,090	12,684	25,774
21	67	1	2	8,025	7,717	15,742
22	34	1	2	5,225	5,087	10,312
23	16	1	3	6,070	4,394	10,464
24	74	1	5	10,282	7,638	17,920
25	52	1	2	5,160	5,222	10,382
Mean ± SD	40 ± 16		3 ± 1	7,753 ± 3,472	7,166 ± 3,439	14,919 ± 6,740

APs = accessory pathways; SD = standard deviation.

component charges in each group revealed that the mean hospital charge per patient in the radiofrequency group was \$7,753 ± \$3,472 compared with \$37,708 ± \$10,179 in the surgical group ($p < 0.0001$). The mean physician charge per patient in the radiofrequency group was \$7,166 ± \$3,439 compared with \$15,557 ± \$3,149 in the surgical group ($p < 0.0001$). In the radiofrequency group, the physician charge consisted almost entirely of the electrophysiologist's fee. In the surgical group, the total physician charge included professional fees billed from electrophysiology, cardiothoracic surgery, anesthesiology and radiology. Although both the hospital and physician charges were significantly lower in the radiofrequency group than in the surgical group, the greater relative reduction occurred in the hospital costs. Figure 1 shows the direct relation between the duration of hospital stay and the total cost of definitive therapy in the radiofrequency and surgical ablation groups. Regression analysis revealed an R-squared value of 0.78 ($p < 0.0001$).

Mean number of days spent in the hospital to achieve accessory pathway ablation was 3.1 ± 1.3 in

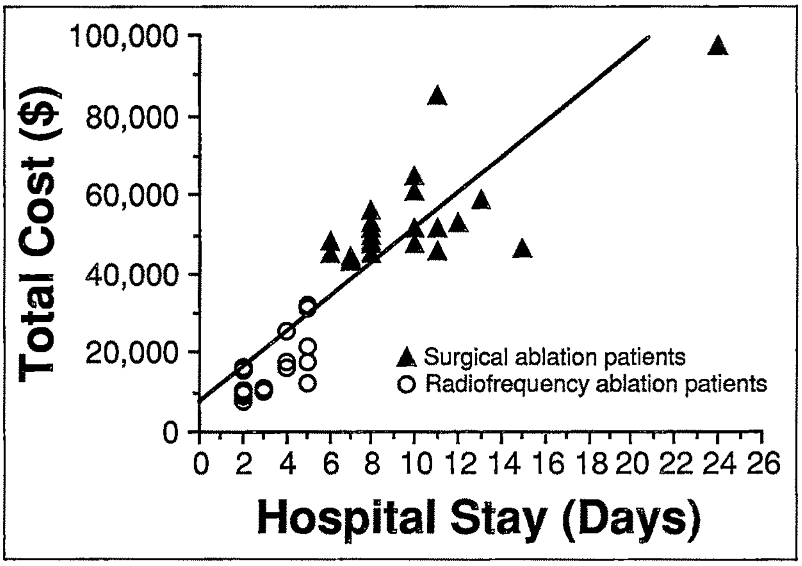

FIGURE 1. Scatter diagram displaying the direct relation between total cost of definitive therapy (dollars) and duration of hospital admission (days) in patients undergoing radiofrequency and surgical ablation of accessory pathways. Regression analysis revealed an R-squared value of 0.78 (p <0.0001).

the radiofrequency group compared with 9.5 ± 3.8 in the surgical group (p <0.0001). Mean number of hospitalizations deemed related to accessory pathway ablation was 1.1 ± 0.3 in the radiofrequency group and 1.2 ± 0.5 in the surgical group (difference not significant). The mean time lost from work was 11 ± 19 days in the radiofrequency group (n = 18) and 55 ± 26 in the surgical group (n = 19) (p <0.0001).

Patient 2[illegible] in the surgical group had the longest admission (24 days) and the highest charges of any patient in the study, with hospital costs of $72,636 and physician fees of $24,892. He was a 20-year-old white man with 2 accessory pathways (left posterolateral and posteroseptal, both manifest). After a baseline electrophysiologic test, he underwent apparently successful accessory pathway ablation. However, within hours, the delta waves reappeared on the 12-lead electrocardiogram and he was brought back to the operating room for a second attempt at surgical ablation. At a follow-up epicardial wire pacing study 1 week later, he was found to have persistent conduction over his posteroseptal accessory pathway and he was treated with flecainide. His postoperative recovery was prolonged due to persistent fevers.

Cost data in uncomplicated cases: Because some of the patients, particularly in the surgical group, had a more complicated course than others, a cost analysis was performed on a subset of 10 patients in each group who had a rapid and uncomplicated postprocedure recovery (patients 5, 8, 11, 13, 15, 16, 19, 22, 24 and 25 in the surgical group, and patients 1, 5, 9, 10, 11, 15, 16, 18, 22 and 25 in the radiofrequency group, Tables I and II, respectively). Total, hospital and physician charges in this subset of patients undergoing uncomplicated radiofrequency and surgical ablation, respectively, were $11,012 ± $2,886 vs $47,726 ± $3,817 (p <0.0001), $5,281 ± $1,266 vs $33,162 ± $3,604 (p <0.0001) and $5,731 ± $1,872 vs $14,564 ± $1,395 (p <0.0001).

DISCUSSION

The main finding of this study is that catheter-mediated radiofrequency ablation accomplishes accessory pathway interruption at a fraction of the cost of surgical ablation. This dramatic reduction in cost is due both to a reduction in hospital costs and physician charges. In the present study, the total cost of therapy in the radiofrequency group was just 28%, hospital costs were 21% and physician fees were 46% of those in the surgical group. Although the most significant factor resulting in lower hospital costs in the radiofrequency group was the shorter hospital stay, other important procedure-related factors included the lack of need for operating room facilities, care in the intensive therapy unit or paramedical ancillary services such as physical therapy and respiratory care. An additional cost-limiting feature of radiofrequency energy is that accessory pathway ablation was achieved during the diagnostic electrophysiologic study in most patients. The lower physician charges in patients undergoing radiofrequency ablation reflect the absence of surgical, anesthesiology and radiology professional fees. When the cost analysis was repeated on a subgroup of patients with uncomplicated procedures, there was still a highly significant difference between the cost of radiofrequency and surgical ablation. Also, the cost-to-charge ratio for hospital services was similar in the 2 groups.

Reduced duration of hospitalization: An important finding of the present study is that radiofrequency ablation results in a marked curtailment in hospital stay. Thus, mean duration of hospital admission was 3 days in the radiofrequency group compared with 9 days in the surgical group. Almost all the patients in the radiofrequency group were walking without difficulty within 12 hours of the procedure, and the only reason for continuing their hospitalization was because of the investigational nature of the procedure. All but 1 of the patients in the radiofrequency group had a very benign post procedure course and could have been discharged from the hospital within 24 hours. Indeed, it is our current practice to discharge patients without complications from the hospital the day after undergoing radiofrequency ablation. In the future, it may even be feasible to perform radiofrequency ablation of accessory pathways on an out-patient basis in selected patients.

General features of radiofrequency ablation that promote cost-containment: There are a number of other general reasons why radiofrequency ablation is associated with cost-containment. The recent dramatic escalation in medical care costs has been attributed, in no small way, to the use of ever-advancing technology in medicine.[5,6] However, radiofrequency ablation contrasts with this general trend in that it represents a new application of an old technology. The technology has been used for several years, for example to treat patients with trigeminal neuralgia, and it's recent application to patients with cardiac arrhythmias has been relatively inexpensive. A comparison with coronary angioplasty is also pertinent. Initial experience with radiofrequency ablation suggests that repeat procedures are required less frequently than is the case with coronary angioplasty and that the initial treatment is usually curative rather than palliative.[2] This feature serves to reduce medical care costs for patients undergoing radiofrequency ablation.

Comparison with previous studies: In a recent study,[7] the costs of catheter-mediated direct-current shock ablation and surgical ablation in the Wolff-Parkinson-White syndrome were compared. In that study,[7] the mean total cost per patient, expressed in 1988 dollar values, was $14,116 ± $4,493 for catheter ablation compared to $34,175 ± $5,434 for surgical ablation ($p < 0.0001$). The mean duration of hospitalization was 6 ± 2 days in the group treated with shock ablation compared with 8 ± 4 days in the group treated surgically (difference not significant). Direct-current shock ablation also had a significant indirect economic advantage as a result of rapid return to work. The present results demonstrate that radiofrequency ablation maintains the cost containment associated with direct-current shock ablation[7] and abbreviates still further the period of hospitalization for patients undergoing definitive therapy. It also permits rapid return to work with beneficial indirect economic effects.

Comparison of the cost of radiofrequency ablation and drug therapy: For the purposes of comparison, we examined the cost of treatment with a representative antiarrhythmic drug, propafenone, in a hypothetical patient with an accessory pathway and recurrent supraventricular tachycardia. In the case of a dose of 225 mg three times daily and a 3-month prescription, refilled 4 times, the annual cost is $1,000; if 1 year's supply is dispensed at once the cost is $985. Thus, the annual cost for this drug alone is approximately $1,000 and this does not take into consideration the cost of a diagnostic electrophysiologic test and electropharmacologic testing, visits to a physician or emergency room, lost productivity because of time away from work, the inconvenience associated with taking medication 3 times per day, and the possible adverse effects and lifestyle restrictions. Based on these figures, radiofrequency ablation would pay for itself in ≤ 15 years, and any patient who required drugs for >15 years would save money with radiofrequency ablation. Thus, over the long term, particularly in younger patients, definitive therapy with radiofrequency ablation would appear to be more economical than pharmacologic therapy.

Use of radiofrequency ablation in patients unsuitable for surgical ablation: An interesting finding of the present study is the significant difference in age and duration of symptoms between patients undergoing radiofrequency and surgical ablation of accessory pathways. Thus, mean age and symptom duration in the radiofrequency group was 40 ± 16 (range 14 to 74) and 21 ± 17 years, respectively, compared to 30 ± 11 (range 13 to 60) and 11 ± 11 years in the surgical group ($p < 0.01$ and < 0.05, respectively). These data reflect the fact that with radiofrequency ablation we were able to offer a curative procedure to a much broader spectrum of patients and to a group of patients that would not otherwise have been considered suitable candidates for definitive ablation therapy. In addition to their older age, patients in the radiofrequency group had a much higher prevalence of general medical diseases.

Study limitation: A possible limitation of this study is that the cost analysis was retrospective and open. This feature may have introduced a certain bias against surgery. However, a determined effort was made to overcome this potential bias as outlined in the Methods section. In addition, we repeated the analysis on a subgroup of 10 patients with uncomplicated procedures. The cost differentials evident in this subgroup analysis were essentially the same as those present in the overall analysis. Therefore, we feel that the cost data presented are a true and accurate estimate of the cost of these procedures.

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Comparative Cost-Effectiveness Analysis of Quinidine, Procainamide and Mexiletine

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Quinidine and procainamide have the potential for major organ toxicity, whereas mexiletine has been reported to have little risk of organ toxicity, serious proarrhythmia or congestive heart failure, but a relatively high incidence of nuisance side effects. In light of the potential adverse effects of all antiarrhythmic agents as highlighted by the Cardiac Arrhythmia Suppression Trial, the relative cost-effectiveness of these 3 agents was assessed. Based on a review of >1,000 published reports, studies included in the analysis examined ≥1 of these agents in adults, with adequate efficacy or safety data, or both. The majority of studies assessed patients with symptomatic or malignant arrhythmias, or both. Data were analyzed using a decision analysis/cost-effectiveness model. Probabilities were averaged using techniques of meta-analysis. Costs were obtained from a university medical center cost-accounting system and from expected follow-up visits to university clinics. Thirty-seven separate side effects were included in the analysis. In terms of overall cost, 12 months of mexiletine would engender $875, quinidine $1,239 and procainamide $1,911 of expenses. Mexiletine dominates the older agents in terms of cost per successful drug response, a result that holds over a wide range of efficacy and safety data. Analyses demonstrated no increase in all-cause mortality for quinidine and mexiletine over placebo, but a trend toward higher mortality with procainamide. The results suggest that mexiletine is a cost-saving alternative therapy for ventricular arrhythmias when adverse reactions are considered in addition to pharmaceutical costs and treatment efficacy.

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The problem of balancing escalating costs of drug therapy against increased efficacy or decreased adverse reactions suggests cost-utility or cost-effectiveness analysis as a possible tool for drug evaluation.[1-11] One of the therapeutic areas currently receiving scrutiny is that of antiarrhythmic drugs. As a result of the recent report from the Cardiac Arrhythmia Suppression Trial (CAST),[12] the use of this class of agents in asymptomatic patients after myocardial infarction and, perhaps, in other groups as well has undergone a reevaluation. Although it is not certain if these drugs would be of benefit or harm in other groups of patients, there is still concern about adverse reactions to these drugs. Severity and frequency of side effects vary among the available agents, and it is uncertain if initial therapy with 1 agent is preferable to that with another when the effects and costs of adverse reactions are examined. The objective of this study was to establish the relative value of 3 antiarrhythmic agents (quinidine, mexiletine and procainamide), using computer-assisted decision analysis adapted to the study of the differential efficacies, adverse effects and costs associated with these drugs.

METHODS

The decision tree: The decision tree was constructed using Decision Maker (Pratt Medical Group, Boston, Massachusetts)[13]; the basic tree design was parallel for all 3 agents. Three alternative strategies were proposed for the problem, each differing only in the choice of therapeutic agent (quinidine, mexiletine or procainamide). Each strategy gave rise to 2 chance events: (1) whether the therapy was effective; and (2) regardless of the therapeutic efficacy, whether an adverse drug reaction occurred. Thirty-seven adverse drug reactions were

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included in the analysis, because they were commented on in ≥1 article reviewed for the study and resulted in discontinuation of drug therapy, hospitalization, follow-up outpatient care, insertion of a permanent pacemaker, or fatality, giving rise to costs associated with these outcomes. The entire model has 384 unique pathways.

Probabilities: All journals abstracted by MEDLINE® were searched from 1966 to the present for clinical trials from which data could be extracted. Articles were excluded if the study used only 1 dose of drug, contained data on only intravenous drug administration, involved only pediatric patients, contained ill-defined or nebulous efficacy criteria, was an isolated case report or reported insufficient data.

From the review of literature, 132 articles (bibliography available upon request) were selected that met the following criteria for inclusion in the analysis: (1) antiarrhythmic efficacy recorded as a percentage of patients with a certain percent reduction (e.g., ≥70%) in ventricular arrhythmias, or the ability to calculate this figure owing to the availability of all raw data; and (2) side effects recorded as number or percentage of patients with the individual effect for oral quinidine, mexiletine or procainamide. Survival or sudden death was not used as an end point, because data regarding the role of antiarrhythmic drugs for this indication are unknown. From these trials, the only efficacy data consistently available were for arrhythmia suppression. Each study was reviewed by 2 investigators (RJA and DJK), and any discrepancies were resolved through consensus.

To address interstudy differences in patient numbers, sample size-weighted means of all incidences (probabilities) were calculated with dBASE IV (Ashton-Tate, Torrance, California). Using quinidine as the reference standard, relative risks of each parameter were calculated (available upon request). Only those adverse effects reported as needing discontinuation of therapy were included in the analysis. When the adverse reaction was stated specifically not to have occurred, zeroes were entered into the analysis.

For each adverse reaction, the probabilities of drug discontinuation, hospitalization or outpatient treatment, and death were estimated by 3 investigators (WHF, PRK, PJP). They also estimated the number of visits needed for outpatient follow-up treatment, and the probability of permanent cardiovascular pacing for appropriate adverse reactions, such as bradyarrhythmia. Means of these estimates (Table I) were used, and where discrepancies >20% existed consensus was obtained.

Sample size-weighted means were also used to calculate incidence of all-cause mortality. To assess any effects of nonuniformity among patient populations and of study design on outcome of the present evaluation, the data were recalculated according to presence or absence of key study design parameters (including randomization, blinding, crossover design, multicenter nature and retrospective/prospective design) and by specific patient groups (i.e., symptomatic or malignant ventricular arrhythmias, or both, after myocardial infarction, and the elderly).

TABLE I Probabilities of Outpatient or Hospital Treatment

	Outpatient	Hospitalization
Proarrhythmia	0.15	0.85*
Torsades de pointes	0	1.00†
Hypotension	0.67	0.33
Bradyarrhythmia	0.73	0.27‡
Prolonged QT interval	0.67	0.33§
Fever	0.92	0.08
Psychosis	0.92	0.08
Depression	0.78	0.22
Confusion	0.92	0.08
Coordination (ataxia)	0.97	0.03
Abdominal pain	0.95	0.05
Hemolytic anemia	0.55	0.45
Agranulocytosis	0	1.00
Neutropenia	0.78	0.22
Hypersensitivity reaction	0.92	0.08
Hypoprothrombinemia	0.92	0.08
Thrombocytopenia	0.82	0.18
Lupus-like syndrome	0.88	0.12
Dizziness	0.90	0.10
Tremor	0.90	0.10
Anxiety	0.83	0.17
Nausea/vomiting	0.83	0.17
Diarrhea	0.83	0.17
Syncope	0	1.00‖
Headache	0.90	0.10
Hepatomegaly	0.80	0.20
Urticaria	0.83	0.17
Cinchonism	0.95	0.05
Digoxin toxicity	0.83	0.17
Cimetidine interaction	1.00	0

*If hospitalized for proarrhythmia, 0.12 probability of death, and 0.88 probability of PES-directed switch of therapy; † if hospitalized for torsades de pointes, 0.10 probability of death, and 0.90 risk of PES-directed switch of therapy; ‡ if hospitalized for bradyarrhythmia, 0.95 probability of inserting pacemaker, and 0.05 probability of death; § if hospitalized for prolonged QT, 0.93 risk of torsades de pointes, and 0.07 risk of death; ‖ if hospitalized for syncope, 0.35 probability of inserting pacemaker, and 0.65 probability of not inserting pacemaker.

Costs: Inpatient costs were derived from records of patients with an adverse drug reaction in the "E" codes of the ICD classification and were generated by the Clinical Cost Manager (Transition Systems, Inc., Boston, Massachusetts), a cost-accounting system. The Clinical Cost Manager includes such variable costs as nursing care, laboratory tests, procedures and medications. If costs of adverse drug reactions were not identifiable by this method, primary diagnosis was used as a proxy for an adverse drug reaction, where usual length of stay was within the time frame suggested by WHF, PRK and PJP.

Outpatient costs (i.e., visits and required testing) were provided by 3 investigators (WHF, PRK and PJP) from their respective institutions. Physician/consultant fees were all priced at $100 per visit. Inpatient and outpatient costs are listed in Tables II and III, respectively.

TABLE II Hospital Costs Used in the Analysis

Adverse Reaction or Sequelae	Hospital Costs	Physician Costs*	Total Costs
Proarrhythmia	$ 3,915	$ 920	$4,835
Torsades de pointes	$ 3,915	$ 920	$4,835
Hypotension	$ 3,711	$ 500	$4,211
Palpitations	$ 3,915	$ 400	$4,315
Bradyarrhythmia	$ 3,915	$ 530	$4,445
Congestive heart failure	$ 4,890	$ 860	$5,750
Prolonged QT interval	$ 2,177	$ 120	$2,297
Syncope	$ 4,444	$ 670	$5,114
Headache	$ 2,487	$ 270	$2,757
Fever	$ 2,682	$ 570	$3,252
Dizziness	$ 2,273	$ 430	$2,703
Tremor	$ 2,956	$ 290	$3,246
Psychosis	$ 4,966	$ 770	$5,736
Depression	$ 3,952	$ 580	$4,532
Insomnia	$ 2,273	$ 330	$2,603
Coordination difficulties (ataxia)	$ 3,252	$ 540	$3,792
Light-headedness	$ 2,273	$ 350	$2,623
Confusion	$ 4,966	$ 770	$5,736
Weakness	$ 5,807	$ 430	$6,237
Nausea/vomiting	$ 2,967	$ 570	$3,537
Diarrhea	$ 3,318	$ 430	$3,748
Hemolytic anemia	$ 7,132	$ 750	$7,882
Lupus-like syndrome	$ 5,851	$ 680	$6,531
Agranulocytosis	$ 8,008	$1,130	$9,138
Thrombocytopenia	$ 5,924	$1,100	$7,024
Neutropenia	$ 7,821	$ 960	$8,781
Hepatitis	$ 4,451	$ 880	$5,331
Liver function test elevation	$ 3,400	$ 470	$3,870
Renal dysfunction	$ 3,330	$ 570	$3,900
Urticaria	$ 3,651	$ 550	$4,201
Pruritus	$ 2,490	$ 370	$2,860
Blurred vision	$ 2,500	$ 410	$2,910
Cinchonism	$ 2,967	$ 500	$3,467
Hypersensitivity (primarily rash)	$ 3,071	$ 330	$3,401
Digoxin toxicity	$ 3,949	$ 360	$4,309
Pacemaker	$14,000		

Drugs†	AWP (cost/365 days)
MEXITIL (no generic available)	$475
Generic quinidine (Bolar + Rugby)‡	$225
Generic procainamide (Rugby)§	$268

*Including cost of primary physician visit in hospital and physician consults during hospital stay.

†Comparative prescription data [according to the most frequently prescribed agents by manufacturer and strength (source: IMS (NPA), Plymouth Meeting, PA)] and practitioner costs annually (source: Red Book, 1989).

‡54% of total quinidine prescriptions.

§55% of total procainamide prescriptions.

AWP = average wholesale price.

TABLE III Outpatient Costs* Over a 12-Month Period

Bradyarrhythmia	$320
Prolonged QT interval	$320
Fever	$232
Psychosis	$187
Depression	$187
Confusion	$187
Abdominal pain	$293
Hemolytic anemia	$290
Dizziness	$200
Tremor	$160
Anxiety	$160
Ataxia	$187
Nausea/vomiting	$187
Hepatitis	$735
Elevated liver function tests	$653
Diarrhea	$160
Syncope	$573
Headache	$160
Hepatomegaly	$700
Urticaria	$187
Pruritus	$187
Blurred vision	$187
Cinchonism	$160
Hypersensitivity reaction	$187
Digoxin toxicity	$260
Cimetidine interaction	$160
Lupus-like syndrome	$377

*Outpatient visits, labs and other procedures.

Meta-analysis: The technique of meta-analysis was used to adjust for variations in methodologic design, missing data, random error, bias and quality of data.[14-16] Confidence limits on the probabilities were calculated using the binomial approximation, and Hanley's rule of 3/n for the upper limit for true zeroes.[17]

Sensitivity analysis: To test the stability of our results to changes in probabilities and costs, all values were varied over the ranges suggested by 3 investigators (WHF, PRK, PJP) and those reported in the literature.

Cost analysis: Cost analysis uses dollar values for both the cost and outcome measures (in this case, the costs associated with death, hospitalization or outpatient care). Probabilities associated with efficacy and the treatment of potential adverse effects in these general populations were obtained from our database. These were combined with drug, repeat physician office visit and hospital costs. An analysis was performed for each agent, and total health-care costs associated with 1-year treatment were calculated.

Cost-effectiveness analysis: Effectiveness is defined in this model as a nonfatal response to treatment (i.e., arrhythmia suppression). The average cost-effectiveness for each agent was estimated by dividing the value of the cost of treatment by the value of a response thus defined. In analyses where 1 agent engendered the fewest costs and exhibited the greatest effectiveness, the agent was said to dominate the other 2.

RESULTS

Ratios of weighted means: This analysis demonstrated that the efficacy of each regimen was roughly equivalent when defined as suppression of ventricular arrhythmias by $\geq 70\%$. The relative relations for all adverse effects were as expected, with the exception of torsades de pointes. Based on clinical experience, quinidine is more often associated with torsades de pointes, syncope and prolonged QT interval than is procainamide. The original comparison of the incidence of torsades de pointes between quinidine and procainamide showed a relation of 1:5, respectively. However, only 1 study, which was retrospective, contained the original value for procainamide. In a subanalysis of prospective studies only, the incidence of torsades de pointes changed to 0.38% for quinidine and "not reported" for procainamide, a more likely clinical relation.

Cost and cost-effectiveness analyses: In the cost analysis, which entailed combining costs of treatment of adverse effects with drug costs over the 12-patient-month average time on study, mexiletine engendered $875, generic quinidine $1,239 and generic procainamide $1,911 of expenses. If the data are representative of clinical practice, then the induced health-care costs associated with these class IA agents (e.g., those incurred due to treatment of adverse effects) are sufficiently high to overwhelm their direct cost savings for the compound. Indeed, the model is relatively insensitive to the costs of the compounds such that the cost of mexiletine could be almost doubled and this agent would remain the therapy with the best overall cost profile. This results from a relative frequency of serious adverse drug reactions of 1:2.1:2.8 for mexiletine, quinidine and procainamide, respectively. Such a scenario assumes that the side effects are mutually exclusive (i.e., primarily 1 major adverse effect causes drug discontinuation or hospitalization, or both).

A cost-effectiveness analysis, defined in this study as cost per nonfatal response to treatment, translated into average figures of $1,716, $2,382 and $3,901 per successful response for mexiletine, quinidine and procainamide, respectively.

Sensitivity and meta-analyses: Sensitivity analyses demonstrated no difference in the ranking of mexiletine as the least costly and most cost-effective agent. Only if the total annual probability of the occurrence of any adverse drug reaction were much more decreased (i.e., one sixth that reported in the literature) would the acquisition cost of mexiletine render it more costly and less effective. At these decreased levels of side effects quinidine was actually the most cost-effective agent because of its lower acquisition cost.

Linked sensitivity analyses were found to be a reasonable approach to model testing when considering multiple adverse effects of low probability. In this study, totally linked analyses and clusters of types of adverse reactions were examined in order to test the model's stability. For example, if all 8 cardiovascular side effects of mexiletine are increased to the upper limit of their 95% confidence intervals (statistically an implausible situation), the cost of mexiletine rises to $1,241, or $2 more than that of quinidine annually. Moreover, when probabilities of outpatient or hospital treatment were varied by 30% to account for practice variability, there was no difference in the overall study outcome.

TABLE IV Patient/Drug Profiles

Parameter	Drug Quinidine	 Mexiletine	 Procainamide
Number of studies selected*	54	72	30
Mean patient age (yrs)	58.5	58.0	51.0
Mean duration of therapy† (days)	21	69	99
Mean dose (mg/day)	1,228	717	3,219
Cardiac diagnoses‡			
Coronary artery disease (%)	65	64	60
Ischemic heart disease (%)	11	18	10
Hypertension (%)	44	31	23
Mitral valve prolapse (%)	9	13	7
Valvular heart disease (%)	31	46	23
Myocarditis (%)	0	3	3
Rheumatic heart disease (%)	7	6	13
Congenital heart disease (%)	13	9	17
Idiopathic (%)	41	49	33
Congestive heart failure (%)	13	17	3
Acute myocardial infarction (%)	7	10	17
Myocardial infarction (%)	15	26	2
Cardiomyopathy (%)	43	58	40
Premature ventricular contractions (%)	74	68	50
Sustained ventricular tachycardia (%)	6	26	13
Nonsustained ventricular tachycardia (%)	11	22	20
Ventricular tachycardia (%)	41	43	40
Ventricular fibrillation (%)	20	28	40
Unifocal premature ventricular contractions (%)	2	7	3
Multifocal premature ventricular contractions (%)	7	14	10
R on T phenomenon (%)	6	8	10
Couplets (%)	20	25	10
Symptomatic/malignant arrhythmias§	64	69	17
Asymptomatic arrhythmias§	16	16	3
Type/severity of arrhythmia not reported	20	15	80‖

*Numbers total > 132 because some studies compared 2 of the agents;

† Includes only prospective studies (retrospective studies do not specify duration of therapy, just duration of study);

‡ Number of studies mentioning patient with this underlying disease state/total number of studies for this drug (%; numbers for each drug total > 100% because studies included patients with > 1 type of arrhythmia);

§ Percentage of patients;

‖ Not reported probably owing to high percentage of studies with procainamide that were for safety.

Patient profiles: The majority of patients were not treated in the hospital, underwent Holter monitoring rather than programmed electrical stimulation for evaluation of their arrhythmia and had underlying coronary heart disease. Arrhythmia suppression ≥70% was the typical criterion for efficacy. Other patient/drug profile data for comparability of drug groups show the groups to be comparable (Table IV).

Subanalyses: Subanalyses of efficacy criteria, refractoriness and duration of therapy (in addition to assessment of only studies that were prospective, double-blind, placebo-controlled, randomized, of parallel design, and so forth) demonstrated no change in strategy (i.e., mexiletine was still the least expensive of the 3 agents).

The subanalysis of mean duration of therapy (<63 vs ≥63 days) showed that the shorter the duration of the study, the higher the incidence of the adverse effect.

One notable exception was procainamide, where the incidence of lupus-like syndrome was lower (0.09) in studies of shorter duration and was higher (0.16) in those of longer duration. This would be expected, because there is a positive correlation between duration of therapy and presence of lupus-like syndrome.

Similar to previous reports for mexiletine and quinidine,[18] a subanalysis of elderly patients ($\geq$65 years old) demonstrated slight increases in proarrhythmia, bradyarrhythmia, tremor, depression and nausea/vomiting for mexiletine, in hemolytic anemia for procainamide, and in bradyarrhythmia for quinidine.

Because of particular interest in the group of patients with a recent myocardial infarction, a subanalysis of such patients was completed. This analysis included 424 patients (85 for mexiletine, 166 for quinidine, and 173 for procainamide) in 11 studies with recent myocardial infarction as the primary inclusion criterion.

The analysis showed that cardiovascular side effects, in particular, were augmented over the investigation of the entire study population. The evaluation of mexiletine showed a 20-fold increase (0.19 to 4%) in the incidence of hypotension. Mexiletine also demonstrated a threefold increase in the incidence of weakness. For quinidine, the incidences of bradyarrhythmia and prolonged QT interval were increased approximately threefold. For procainamide, the incidences of bradyarrhythmia and fever were increased approximately twofold, whereas those for lupus-like syndrome and hypersensitivity were elevated 1.4- and 1.2-fold, respectively. Numbers for all subanalyses were within the ranges obtained from the literature and thus would not result in a change in the preferred strategy.

Since the availability of results from CAST, there has been an increased awareness of mortality associated with the use of antiarrhythmic agents. Therefore, crude pooled mortality rates were calculated for each agent in comparative studies. Deaths were observed in both treatment and control groups. In the analysis of all patients in comparative studies quinidine (2%, n = 1,259) and mexiletine (1%, n = 1,008) demonstrated mortality comparable to that of placebo (2%, n = 823); mortality with procainamide (4%, n = 560) was approximately twice that of placebo. When only patients with symptomatic or life-threatening ventricular arrhythmias, or both, were studied, the relations for quinidine and mexiletine versus placebo were similar to those for all comparative studies. Interestingly, procainamide exhibited a mortality rate only 1.2 times (5%, n = 482) that of placebo (4%, n = 387).

DISCUSSION

In light of its low propensity toward side effects that increase health-care costs, the present evaluation showed mexiletine to be the most cost-effective antiarrhythmic strategy in an analysis of mexiletine, quinidine and procainamide. The use of mexiletine generated the lowest cost and allowed for the longest maintenance of therapy in comparison with that of the other 2 drugs. This information is especially timely because the CAST results have highlighted the potential, adverse effects of some of the antiarrhythmic agents. Whereas the CAST report focused on increased mortality, side effects are an important concern especially for long-term drug therapy. This is particularly important because drugs with similar efficacy are often selected based on side effects. Indeed, in this study efficacy among the 3 agents evaluated was equivalent, but there were major differences in serious side effects. Our evaluation corroborates the observations of Morganroth and Bigger[19] who recently characterized mexiletine as having a relatively high risk of noncardiac side effects, but little or no risk of organ toxicity, early occurring serious proarrhythmia and congestive heart failure.

A shortcoming of this study is one that is inherent with the use of retrospective data; i.e., only author interpretations of data were available. Overlapping definitions of adverse effects (e.g., syncope, prolonged QT interval and torsades de pointes) and the fact that not all studies evaluated all parameters are additional variables that may have affected incidences of adverse effects. Furthermore, as mentioned previously, only those adverse effects specifically noted as needing discontinuation of therapy were included in the analysis. This method tended to underestimate the probability of an adverse reaction and thus may have deflated all values in the analysis. However, the degree of deflation should be approximately the same for each drug selected, and sensitivity analyses over the possible range of values were used to correct for any underestimation.

Pratt and Moye[20] recently detailed other confounding variables when using published literature for comparative drug analyses in their review of the CAST study. Nonetheless, "the strength of analyzing the entire antiarrhythmic drug database is preferable to the alternative of analyzing reports from individual clinical centers where sample sizes are small."[20] To limit any inherent biases in retrospective examination of retrospective data and to address nonuniformity of study design among those assessed, the model was reevaluated using only data from prospective, placebo-controlled, double-blind, randomized studies. While these cost and cost-effectiveness reevaluations resulted in slight quantitative differences, the qualitative outcomes were similar to those we noted when data were incorporated from all studies.

In addition, the tendency to publish primarily positive studies may impart literature bias. However, this would be expected with the 3 drugs studied. Furthermore, there were some negative studies, and approximately 10% of the articles compared ≥2 of the study drugs. Despite some limitations, the methodology used in the present study is accepted technique for establishing cost-effectiveness.[5,10]

An additional analysis in this study showed no difference in all-cause mortality among patients with symptomatic arrhythmias when quinidine, mexiletine and procainamide were compared with placebo. This is in contrast to the meta-analysis involving quinidine for therapy of atrial fibrillation reported by Coplen and et al[21] in which a higher mortality with quinidine was observed. The present study involves a much larger number of patients and is the first such data for those with ventricular arrhythmias. In these patients, antiarrhythmic drugs were not associated with an increased risk of death.

Finally, although mexiletine would be expected to have similar efficacy and be safer than quinidine and procainamide, the present study is the first attempt at quantifying the costs of this relationship. The decision-analytic method used in this study is valuable because it combines an extensive published data source (the literature) with current practice methods. As clinicians are being increasingly called on to evaluate risk-benefit of therapies, cost-effectiveness analysis will become a key method of identifying the most appropriate therapy for particular patient populations and of reducing overall health-care costs.

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Reproducibility and Relation to Mean Heart Rate of Heart Rate Variability in Normal Subjects and in Patients with Congestive Heart Failure Secondary to Coronary Artery Disease

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Before heart rate (HR) variability can be used for predictive purposes in the clinical setting, day-to-day variation and reproducibility need to be defined as do relations to mean HR. HR variability and mean HR were therefore determined in 2 successive 24-hour ambulatory electrocardiograms obtained from 33 normal subjects (age 34 ± 7 years, group I), and 22 patients with coronary disease and stable congestive heart failure (CHF) (age 59 ± 7 years, group II). Three measures were used: (1) SDANN (standard deviation of all mean 5-minute normal sinus RR intervals in successive 5-minute recording periods over 24 hours); (2) SD (the mean of the standard deviation of all normal sinus RR intervals in successive 5-minute recording periods over 24 hours); and (3) CV (coefficient of variation of the SD measure), a new measure that compensates for HR effects. Group mean HR was higher and HR variability lower in group II than in group I (80 ± 10 vs 74 ± 9 beats/min, p <0.04). Mean group values for HR and HR variability showed good correlations between days 1 and 2 (mean RR, r = 0.89, 0.97; SDANN, r = 0.87, 0.87; SD, r = 0.93, 0.97; CV, r = 0.95, 0.97 in groups I and II, respectively). In contrast, considerable individual day-to-day variation occurred (group I, 0 to 46%; group II, 0 to 51%). Low HR variability values were more consistent than high values. SDANN and SD correlated moderately with HR in both groups (r = 0.50 to 0.64). The CV measure minimizes HR effects on HR variability. In conclusion (1) mean group differences in HR variability between normal subjects and patients with CHF are highly reproducible, but considerable day-to-day variations may occur in some subjects, particularly normal persons with high HR variability; (2) mean HR is higher and HR variability lower in patients with CHF; and (3) mean HR must be considered when interpreting changes in HR variability. The CV measure minimizes this problem.

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Computerized analysis of 24-hour ambulatory electrocardiographic recordings can provide quantitative measurements of heart rate (HR) variability. Recent studies have shown that low HR variability is an independent risk factor of mortality in patients after myocardial infarction and in patients with coronary artery disease.[1,2]

Although most studies have focused on group comparisons,[1–4] cut-off values of HR variability have been proposed for purposes of risk stratification in individual patients.[1,2] However, because all reported HR variability values have been computed from single 24-hour ambulatory electrocardiographic recordings, the day-to-day variation is unknown. A correlation between mean HR and HR variability within study populations has been described,[1,2] but the impact of changes in HR on HR variability, both for groups and individual patients, also is not known. To gain insight into these problems we examined (1) the day-to-day variation and reproducibility of frequently used HR variability measurements assessed from 2 successive 24-hour ambulatory electrocardiographic recordings in healthy young subjects and in patients with congestive heart failure

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(CHF) secondary to coronary artery disease, (2) the relation of HR variability and mean HR, and (3) intergroup differences in HR variability and mean HR in normal subjects and patients with CHF.

METHODS

Study group: Two population groups were studied: Group I consisted of 33 healthy volunteers, 19 men and 14 women without known cardiac disease, systemic hypertension or diabetes mellitus. Group mean age was 34 years (range 24 to 54). All had normal results on physical examination and a normal 12-lead electrocardiogram at rest. Contraceptives and occasional nonsteroidal antiinflammatory agents were the only medications given. Group II consisted of 22 outpatients, 18 men and 4 women, aged 45 to 71 years (mean 59) with coronary artery disease and prior myocardial infarction complicated by stable New York Heart Association class II to III CHF, and treated with digoxin and diuretics. CHF was documented by history, physical examination, chest x-ray and right-sided cardiac catheterization (cardiac index <2.7 liters/min/m^2 or pulmonary capillary wedge pressure >15 mm Hg at rest, or both). Patients with diabetes and chronic obstructive lung disease were excluded, as were patients with atrial fibrillation, sick sinus syndrome, atrioventricular block and paced rhythms.

Data collection: All subjects underwent two 24-hour ambulatory electrocardiographic recordings using Marquette model 8500 AM 2-channel recorders. Recordings were obtained on 2 consecutive days for all group II patients (CHF). Recordings from 29 of 33 group I subjects (normal) also were obtained on 2 consecutive days. In the remaining 4 subjects, recordings were obtained 9 to 29 days apart. There were no interim changes in clinical state. Recordings were analyzed using a Marquette 8000 computerized Holter system, which classifies each beat as to site of origin. The beat classification was overread manually and corrected where necessary. Each RR interval during the 48-hour period was determined. The data were then transferred to Digital Equipment VAX computer and Cambridge Digital 11/73 systems for further analysis.

The software used to measure HR variability was developed in our laboratory.[3–6] It determines the mean ± standard deviation (SD) of the sinus RR intervals for each 5-minute period during the recording period, and subsequently computes their mean value. In instances in which sinus rhythm is interrupted by ectopy, the program eliminates 1 RR interval preceding, and 2 RR intervals following, nonsinus beats.

Three HR variability determinations were obtained for each subject: (1) the "SDANN" measure (or the standard deviation of all mean 5-minute "normal" sinus RR intervals, i.e., sinus RR intervals without intervening ectopic beats, over 24 hours[2,3]); (2) the "SD" measure (defined as the mean of the standard deviations of all normal sinus RR intervals during successive 5-minute recording periods over 24 hours[3]); and (3) a new measure, the "CV" measure (or coefficient of variation of the SD, which is obtained by dividing the SD value for each 5-minute period by the mean RR interval for that period, and then averaging all the 5-minute CV values over 24 hours).

Data analysis and statistical methods: The following analyses were performed: First we tested day-to-day variation in, and reproducibility of, HR variability by comparing individual and mean group values for the 2 days. The results were expressed as mean ± SD of the percent differences between the days. The overall comparability of the two 24-hour recording periods was assessed by comparing mean RR for days 1 and 2 for each group. The Pearson product-moment correlation coefficient was then calculated to describe day 1 to day 2 relation for HR and HR variability. Second, we examined correlations between mean HR and HR variability for the 2 study groups and used the least-squares regression method to define the relation. The 2-way analysis of variance was used to test for differences in mean group values for the RR interval and HR variability, and for differences between men and women. Third, we compared mean HR and HR variability of normal subjects and patients with CHF.

The SAS statistical package version 6.03 was used for all statistical analyses.[7] Normality of distribution of the data was tested using the Shapiro-Wilk statistic. When normally distributed, data are presented as mean ± SD. Differences were considered significant at $p < 0.05$. In cases in which the data were not normally distributed, significance was determined by a rank sum test rather than a *t* test.

RESULTS

Day-to-day variation in mean heart rate and heart rate variability: GROUP I (NORMAL SUBJECTS): Table I lists demographic data for group I subjects, mean RR intervals, and HR variability data for the two 24-hour periods. For group I subjects as a whole, mean HR was nearly equal on day 1 (RR = 818 ± 97 ms) and day 2 (RR = 811 ± 94 ms). The mean RR interval of individual subjects, however, exhibited much greater day-to-day variation (0 to 13%).

Correlation between HR variability values for the 2 days was high for all 3 measures tested; r values ranged from 0.87 for the SDANN, to 0.93 for the SD and 0.95 for the CV (Figure 1). The mean SDANN num-

TABLE I Demographics, Mean RR Intervals and Heart Rate Variability Data from Two Consecutive 24-Hour Electrocardiographic Recordings in Group I (normal) Subjects

Pt. No.	Age (yr) & Sex	Mean RR (ms)			SD (ms)			CV (ms)			SDANN (ms)		
		Day 1	Day 2	Δ%	Day 1	Day 2	Δ%	Day 1	Day 2	Δ%	Day 1	Day 2	Δ%
1	54 F	871	842	3.4	77	71	7.8	8.7	8.2	6.0	173	184	5.9
2	23 M	983	944	4.0	117	109	7.0	11.5	11.2	2.6	250	220	11.9
3	23 F	746	781	4.6	65	65	0.8	8.5	8.1	4.5	122	151	24.3
4	23 F	616	576	6.6	40	32	20.8	6.4	5.5	13.7	101	59	41.2
5	35 M	996	914	8.3	94	87	6.5	9.3	9.4	1.5	231	201	13.0
6	23 M	798	855	7.1	136	127	6.6	15.7	14.2	9.4	236	276	17.0
7	27 M	836	924	10.5	99	113	14.2	11.3	12.0	5.7	217	181	16.6
8	35 M	1,020	1,028	0.8	83	87	4.6	8.2	8.4	2.9	120	148	23.0
9	3[illegible] M	938	888	5.4	134	108	19.9	13.7	11.5	16.2	199	199	0.2
10	23 M	807	814	0.8	71	73	3.4	8.7	9.0	3.2	150	146	2.7
11	24 F	683	699	2.3	53	55	3.8	7.6	7.8	2.5	115	113	2.3
12	35 M	820	810	1.2	48	51	5.4	6.0	6.3	5.3	79	90	14.2
13	47 M	875	906	3.5	69	68	0.9	7.8	7.5	4.1	113	117	3.5
14	3[illegible] F	751	727	3.1	53	51	3.4	7.0	6.9	0.4	106	104	2.2
15	36 F	726	708	2.5	82	74	9.4	11.3	10.6	6.8	149	128	14.0
16	38 F	761	773	1.7	63	67	6.4	8.2	8.7	5.2	159	164	3.1
17	42 M	826	826	0.0	65	67	3.3	7.9	8.1	2.4	91	94	3.2
18	4[illegible] M	792	733	7.4	57	57	0.4	6.8	7.3	6.5	166	156	5.9
19	25 M	814	815	0.0	85	83	1.3	9.5	9.6	0.8	208	217	4.7
20	2[illegible] F	777	850	9.5	90	114	25.9	11.0	12.6	15.0	139	146	4.5
21	38 F	807	733	9.1	71	53	25.7	8.5	7.2	15.5	164	89	45.8
22	24 M	985	855	13.2	128	112	12.5	12.9	12.7	1.1	190	172	9.6
23	28 M	791	806	2.0	64	62	3.3	8.0	7.7	3.6	135	105	22.1
24	30 M	913	970	6.3	91	104	14.0	9.9	10.7	7.5	175	195	11.5
25	42 F	799	791	1.0	68	71	4.3	8.4	8.8	4.8	106	104	1.4
26	37 M	771	768	0.5	51	51	1.2	6.6	6.6	0.0	91	124	37.0
27	35 F	639	651	1.9	47	44	6.8	7.2	6.6	8.1	94	93	1.6
28	27 F	755	726	3.8	66	62	6.8	8.6	8.4	2.7	104	93	9.9
29	30 M	720	741	2.9	57	55	2.3	7.7	7.4	4.0	135	124	8.5
30	40 F	815	820	0.7	69	66	4.8	8.4	8.0	4.9	131	105	20.1
31	44 M	918	875	4.7	85	78	8.8	9.2	8.7	5.2	186	183	1.5
32	29 M	869	847	2.6	58	60	3.4	6.7	7.2	6.4	143	115	19.3
33	36 F	788	757	3.9	84	74	12.0	10.5	9.6	8.6	137	130	5.0
Mean	34 58% M	818	811	4.1	76	74	7.8	9.0	8.9	5.7	149	143	12.3
± SD	± 7	± 97	± 94	± 3.3	± 25	± 23	± 6.9	± 2.2	± 2.1	± 4.3	± 46	± 48	± 11.7

CV = coefficient of variation of the SD measure; Mean ± SD = mean ± standard deviation; SD = mean of the standard deviation of all normal sinus RR intervals during successive 5-minute recording periods over 24 hours; SDANN = standard deviation of all mean 5-minute normal sinus RR intervals over 24 hours; Δ% = (day 2 mean heart rate − day 1 mean heart rate/day 1) × 100.

ber for group I subjects showed the largest day-to-day variation: 149 ± 46 ms on day 1 and 143 ± 48 ms on day 2. Day-to-day variability was lower for mean SD values (76 ± 25 and 74 ± 23 ms), and least for CV values (9.0 ± 2.2 and 8.9 ± 2.1 ms) on days 1 and 2, respectively.

Individual subjects had more marked day-to-day variation in HR variability than did the corresponding groups as a whole irrespective of the measure used, ranging from a low of 0% to a high of 46% for the SDANN, from 0 to 26% for the SD, and from 0% to 16% for CV values. Large day-to-day variation in HR variability in a given patient determined by 1 measure did not necessarily imply similarly high degrees of variability using the other measures (Table I).

GROUP II (PATIENTS WITH CONGESTIVE HEART FAILURE): Table II lists demographic and HR variability data for group II patients. Mean RR intervals on day 1 (762 ± 90 ms) and day 2 (779 ± 100 ms) differed only minimally (r = 0.97). Day-to-day variation in mean RR interval for individual patients with CHF (0 to 8.3%, mean 2.8 ± 2.5) was less than for normal subjects (0 to 13.2%, mean 4.1 ± 3.3).

HR variability was even more reproducible for patients with CHF than for normal subjects: mean SD values for days 1 and 2 averaged 36 ± 16 and 38 ± 17 ms; mean SDANN, 87 ± 35 and 87 ± 38 ms; and mean CV, 4.7 ± 1.9 and 4.8 ± 1.9 ms, respectively. All HR variability measures exhibited high Pearson correlation coefficients: SDANN = 0.87; SD and CV = 0.97 (Figure 2).

Day-to-day variation in HR variability for individual patients with CHF was similar to that for normal subjects: SD, 1 to 28% (mean 8.5 ± 7.3); SDANN, 0 to 51% (mean 13.8 ± 13.5); and CV = 1 to 18% (mean 7.9 ± 5.2).

TABLE II Demographics, Mean RR Intervals and Heart Rate Variability Data from Two Consecutive 24-Hour Electrocardiographic Recordings in Group II Patients with Congestive Heart Failure

Pt. No.	Age (yr) & Sex	Mean RR (ms) Day 1	Mean RR (ms) Day 2	Mean RR (ms) Δ%	SD (ms) Day 1	SD (ms) Day 2	SD (ms) Δ%	CV (ms) Day 1	CV (ms) Day 2	CV (ms) Δ%	SDANN (ms) Day 1	SDANN (ms) Day 2	SDANN (ms) Δ%
1	71 M	636	668	5.0	28	25	10.1	4.3	3.7	13.9	92	90	2.2
2	65 M	936	1008	7.7	64	69	7.3	6.7	6.9	2.5	157	129	17.9
3	45 M	780	779	0.1	63	57	9.4	8.2	7.5	9.1	93	82	12.1
4	48 M	697	707	1.4	44	41	6.4	6.4	5.9	7.5	92	78	15.6
5	64 F	731	757	3.7	18	18	1.1	2.4	2.4	2.0	64	63	1.7
6	60 M	750	734	2.1	12	12	3.4	1.6	1.7	5.7	38	36	3.2
7	54 F	870	943	8.3	58	63	9.2	6.6	6.7	1.1	154	157	1.8
8	68 M	878	900	2.5	41	44	8.8	4.6	5.0	7.5	106	85	19.7
9	56 M	746	757	1.5	32	32	0.6	4.5	4.5	0.7	99	99	0.1
10	52 M	798	814	2.0	21	25	17.6	2.6	3.0	15.6	49	69	39.3
11	68 M	797	841	5.6	49	62	28.2	6.0	7.0	17.2	126	189	50.6
12	67 M	834	834	0.0	40	44	8.7	4.9	5.4	10.7	92	87	4.7
13	65 M	587	591	0.8	13	13	1.5	2.2	2.2	1.4	38	31	18.4
14	63 M	855	859	0.5	24	26	9.2	2.8	3.1	9.7	40	38	6.0
15	55 M	709	693	2.3	47	50	6.2	6.6	7.2	8.6	81	98	20.5
16	51 M	814	794	2.4	62	62	1.0	7.5	7.9	4.5	135	130	3.7
17	58 M	684	737	7.7	34	43	26.1	4.9	5.8	17.9	107	89	16.8
18	56 M	700	707	0.9	42	39	7.9	6.0	5.5	9.5	90	85	5.3
19	52 M	881	890	0.9	34	36	4.7	3.9	4.0	4.7	88	82	6.9
20	66 M	737	743	0.8	23	24	8.0	3.1	3.3	6.5	58	79	37.2
21	62 F	693	715	3.1	32	31	1.6	4.6	4.4	3.9	62	71	14.6
22	53 F	651	670	3.0	17	15	10.5	2.7	2.3	13.2	59	55	6.1
Mean	59 82% M	762	779	2.8	36	38	8.5	4.7	4.8	7.9	87	87	13.8
± SD	± 7	± 90	± 100	± 2.5	± 16	± 17	± 7.3	± 1.9	± 1.9	± 5.2	± 35	± 38	± 13.5

Abbreviations as in Table I.

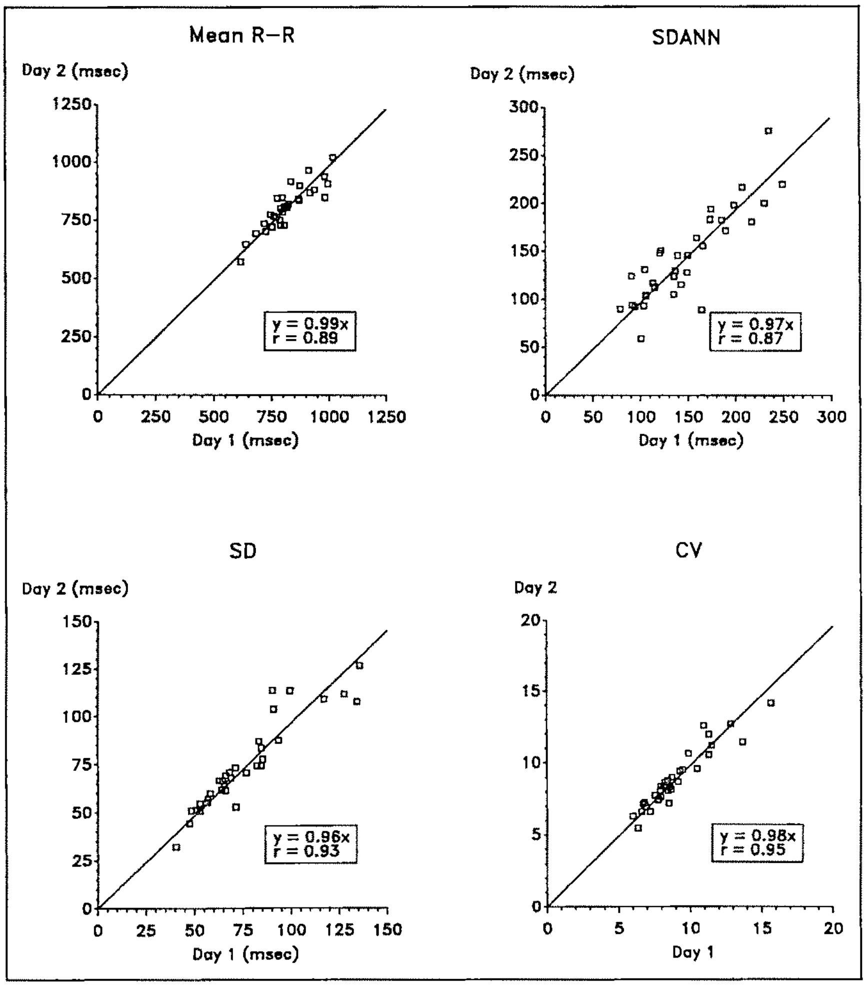

FIGURE 1. Variability of mean RR interval, and heart rate variability determined using SDANN, SD and CV measures on 2 consecutive days in 33 normal subjects (group I). See text for discussion. CV = coefficient of variation of the SD measure; SD = mean of the standard deviation of all normal sinus RR intervals during successive 5-minute recording periods over 24 hours; SDANN = standard deviation of all mean 5-minute normal sinus RR intervals over 24 hours.

Heart rate variability reproducibility: Reproducibility of all HR variability measures tested was also very similar for the 2 groups as a whole; the CV measure showed the smallest day-to-day variation and the highest correlation coefficient. Use of the CV measure resulted in significantly fewer patients with day-to-day variations ≥20%, the chi-square test for SD versus CV having an approximate p value of 0.05 and for CV versus SDANN $p < 0.01$. HR variability values in the range associated with increased risk of mortality$^{1-4,6}$ (i.e., SDANN ≤50 ms and SD ≤30 ms) showed less day-to-day variation (i.e., were more reproducible) than the high HR variability values in normal subjects. In 3 of the 4 patients with a day 1 SDANN <50 ms, the day 2 SDANN also was <50 ms. In the fourth subject it was only just slightly higher (69 ms). In 4 of 6 patients with SDANN >100 ms on day 1, the value remained >100 ms on day 2 and decreased only moderately (to 85 to 89 ms) in the remaining 2 (Table II). In no patient did SDANN change from >100 to <50 ms between the 2 monitorings. All 8 patients with a SD value ≤30 ms on day 1 had similarly low values on day 2. Conversely, there were no changes from >30 to ≤30 ms.

Relation between mean heart rate and heart rate variability: GROUP I (NORMAL SUBJECTS): Despite considerable interindividual differences in SD and SDANN values for given mean RR intervals, there was a moderate but significant correlation between the mean 24 hour RR interval and the SD and SDANN values ($r = 0.64$ and 0.54, respectively) (Figure 3). In contrast, CV values did not correlate with mean RR.

GROUP II (PATIENTS WITH CONGESTIVE HEART FAILURE): Individual CHF patients with identical or comparable mean 24-hour HR often exhibited considerable differences in HR variability determined by SD and SDANN measures. Although group SD and SDANN values were lower for those with CHF than for normal subjects (Figure 4), persons in the 2 groups exhibited a similar range of HR variability. Relation between 24-hour mean RR intervals and mean SD and SDANN values were similar to those in group I ($r = 0.52$ and 0.50, respectively) (Figure 3).

Differences in mean heart rate and heart rate variability between group I and II subjects: Group II patients (CHF) had a higher mean HR than group I subjects (normal): average mean 48-hour RR interval = 770 ± 94 and 814 ± 93 ms for the 2 groups, respec-

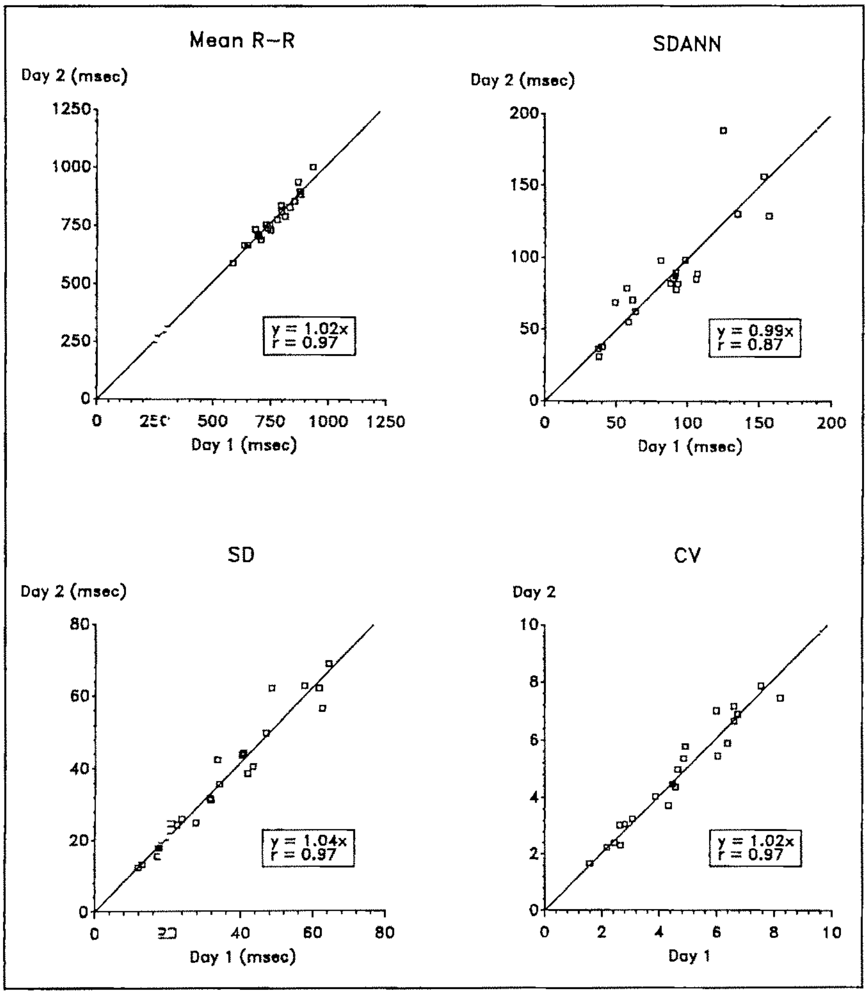

FIGURE 2. Variability of mean RR interval, and heart rate variability determinations using SDANN, SD and CV measures on 2 consecutive days in 22 patients with congestive heart failure (group II). See text for discussion. Abbreviations as in Figure 1.

tively, but the differences did not reach significance (p ≅ 0.09). Day 1 HR variability was significantly lower for patients with CHF than for normal subjects, irrespective of the measure used: SD 36 ± 16 vs 76 ± 25 ms (p <0.001); CV 4.7 ± 1.9 vs 9.0 ± 2.2 (p <0.001); SDANN 87 ± 35 vs 149 ± 46 ms (p <0.001), respectively (Figure 4). SD and CV values were not normally distributed, so significance was determined using the rank sum test. Despite the large overall group differences, there was a considerable overlap between subjects in the 2 groups. Day 2 findings were similar.

Gender-related differences: Mean HR was significantly higher in women than in men (mean RR interval = 748.8 ± 69.4 vs 862.9 ± 77.9 ms, p <0.01). HR variability determinations using the SDANN measure were significantly lower for women than for men; the SD measure approached significance. In contrast, CV values did not differ for the 2 groups (Table III).

DISCUSSION

Our study revealed the following results: (1) Mean group HR variability values for both normal subjects and patients with heart disease were highly reproducible as were mean group differences. However large day-to-day variations in SD, SDANN and CV values occurred in some subjects, particularly those with high HR variability. In contrast, patients with low HR variability values had much less day-to-day variation. (2) Mean HR was higher and HR variability lower in patients with CHF than in normal subjects. (3) Mean HR also was higher and HR variability lower in women than in men. (4) Mean HR must be considered when interpreting differences in HR variability. Use of the CV measure minimizes this problem.

Day-to-day variance in mean heart rate and heart rate variability: Days 1 and 2 mean HR determinations were nearly equal for the 2 groups. Mean group values for all HR variability measures studied also were highly reproducible (r = 0.87 to 0.97, Tables I and II, Figures 1 and 2). In contrast, considerable day-to-day variations in HR variability were noted in individual subjects, ranging from 0 to 46% in the normal and 0 to 51% in the CHF group, respectively. Maximal day-to-day differences in HR variability were lowest for CV and highest for SDANN values. That the CV measure was the most reproducible of the 3 support the view that day-to-day variations in HR variability partly reflect changes in HR, presumably secondary to varia-

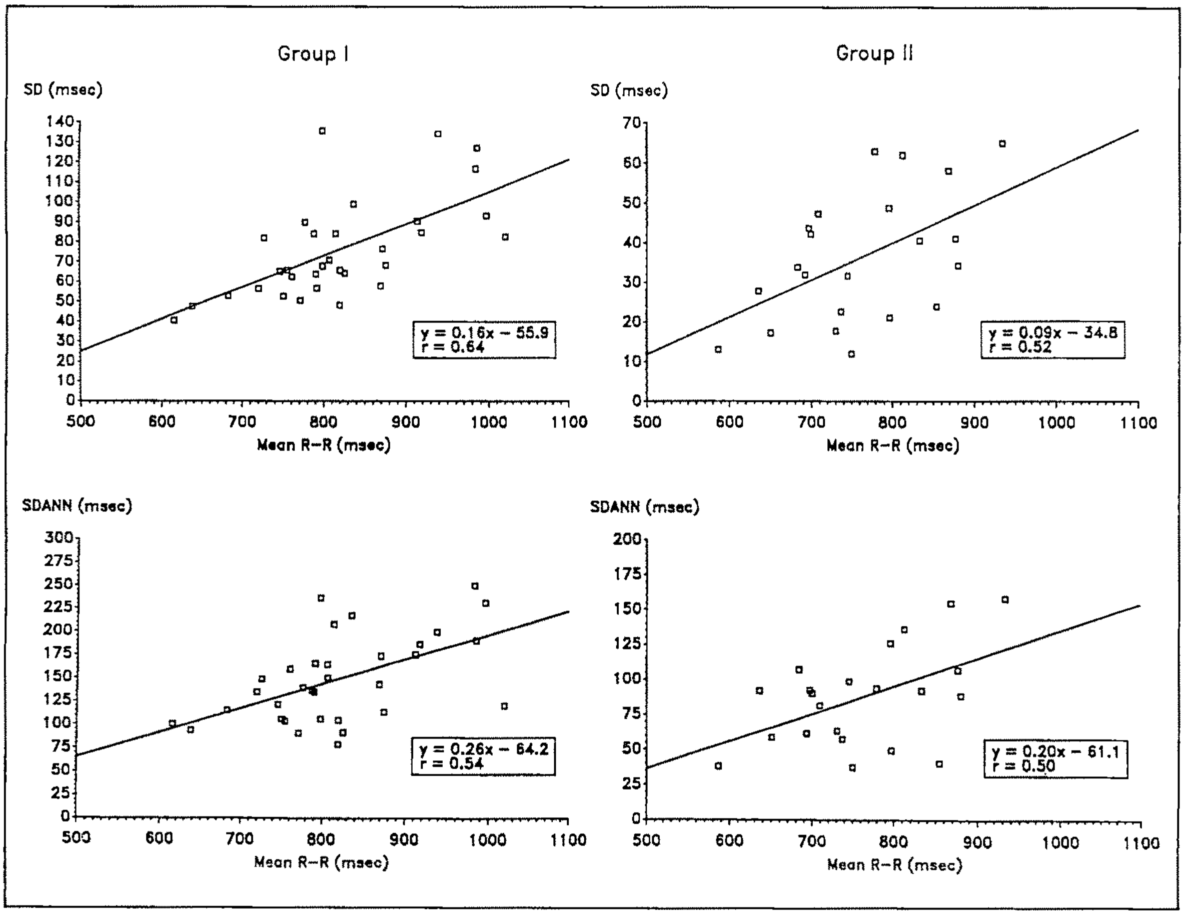

FIGURE 3. Correlation of heart rate (expressed as mean RR interval) and heart rate variability determined using SD and SDANN measures on day 1 in 33 normal subjects (group I) and 22 patients with congestive heart failure (group II). See text for discussion. Abbreviations as in Figure 1.

tions in autonomic tone in conjunction with changes in physical activity, emotional state, and so forth. However, use of the CV measure for identifying patients at increased risk of dying remains to be determined by clinical trial

TABLE III Male/Female Mean Heart Rate and Heart Rate Variability in Normal Subjects

	Men (n = 19)		Women (n = 14)		
	Mean	SD	Mean	SD	p Value
Age (years)	33.0	6.7	34.4	8.1	0.5813
Mean RR (ms)	862.9	77.9	748.8	69.4	0.0001
Mean HR (beats/min)	70.1	6.3	80.9	8.2	0.0002
SD (ms)	82.7	25.8	65.3	16.1	0.0336
SDANN (ms)	162.5	49.8	123.6	27.2	0.0128
CV (%)	9.3	2.4	8.5	1.6	0.2748

HR = heart rate; other abbreviations as in Table I.

Day-to-day variation of 1 HR variability measure did not always parallel that for the other measures, e.g., large changes in SD in group I subjects (nos. 4 and 21) were paralleled by similar changes in SDANN, whereas subjects 9 and 20, with approximately the same changes in SD, exhibited much smaller variations in SDANN values. Because we carefully excluded 1 RR interval preceding and 2 RR intervals following ectopic beats, as well as subjects with atrioventricular block, changes in ectopic frequency or atrioventricular conduction between days 1 and 2 could not be a factor. Differences in the frequency bands of the power spectrum reflected by the SD and SDANN measures represent 1 possible explanation. Myers et al[11] showed the SD measure to be sensitive to spectral components B-D, a wide frequency band (0.05 to 0.50 Hz) that includes the component associated with vagally mediated

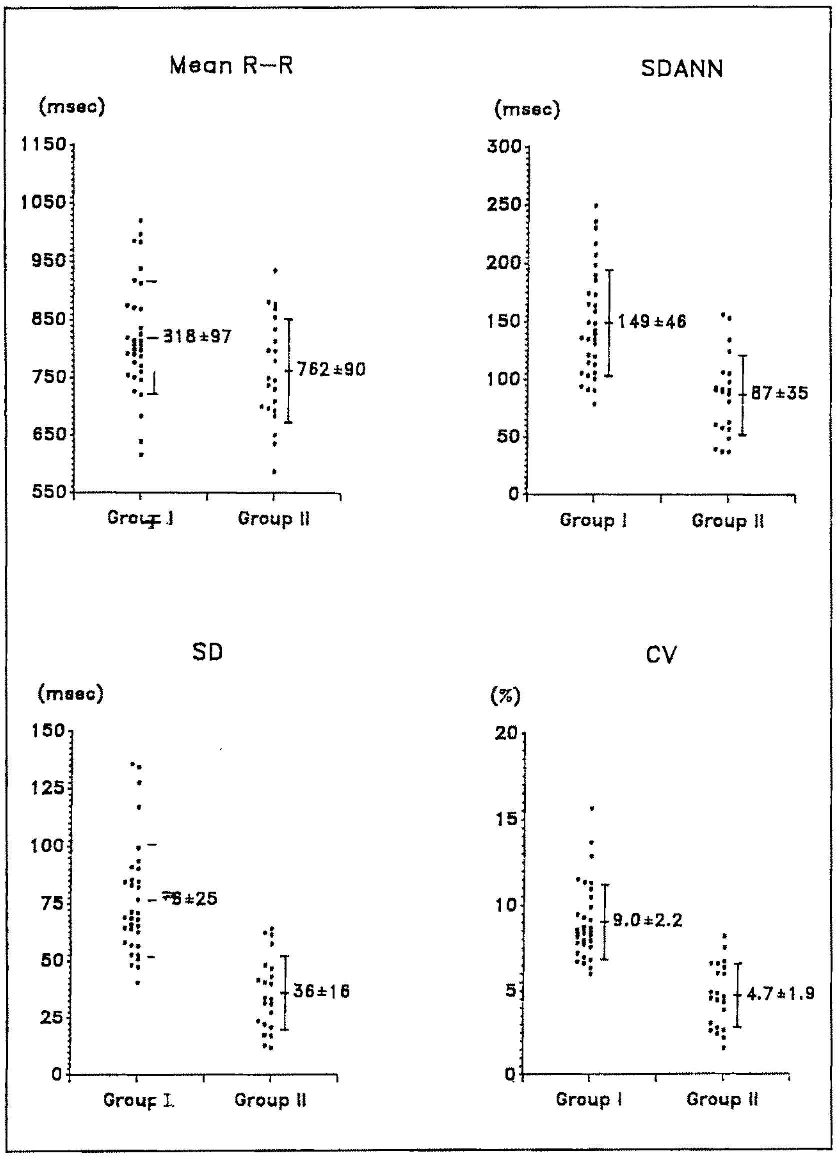

FIGURE 4. Dot plots comparing day 1 mean RR interval and heart rate variability (SDANN, SD and CV measures) for normal group I subjects and group II patients with congestive heart failure. See text for discussion. Abbreviations as in Figure 1.

respiratory rate changes. In contrast, the SDANN measure is much more sensitive to component A of the power spectrum, a much narrower frequency band (0.0167 to 0.05 Hz) that is associated with the vasomotor and renin-angiotensin control systems[12] and is sensitive to posture and activity changes affecting HR by nonvagal mechanisms.

Relations between mean heart rate and heart rate variability: In accordance with other studies,[1,2] we found a correlation between mean RR interval and HR variability determinations using the SD and SDANN measures for both groups I and II; the correlation coefficients of 0.54 and 0.50 for the SDANN measure were comparable to that ($r = 0.52$) reported by Kleiger et al[1] for postmyocardial infarction patients. Rich et al[2] reported an inverse correlation ($r = -0.38$) between HR and SDANN in patients undergoing cardiac catheterization. In our study, the correlation was similar for both groups (Figure 3). For a given HR, HR variability of normal subjects was higher than that of patients with heart disease. To the extent that HR variability reflects parasympathetic activity, this observation supports conclusions that parasympathetic control may be defective in patients with heart disease.[5,13]

Group differences in mean heart rate and heart rate variability: Mean RR interval was shorter and HR variability (all measures) lower in patients with CHF than in normal subjects. This agrees with findings by Casolo et al.[8] However, differences in the HR variability measures used preclude direct comparisons. In addition, patients with CHF in their study did not take digitalis glycosides. This contrasts with our own patients with CHF, all of whom were taking digoxin. Digitalis glycosides are known to enhance vagal activity[9,10] and, as such, would be expected to increase HR variability, which largely reflects parasympathetic activity. Therefore, the use of digoxin would, if anything, tend to minimize differences in HR variability between the 2 groups, which nevertheless were significant for all HR variability measures tested.

It is pertinent that the mean age of the normal subjects was much lower than that of the patients with CHF, a condition that complicates the interpretation of the data. Since HR variability would be expected to be higher in young than in middle-aged and elderly subjects,[14] the extent to which age difference, per se, underlies observed HR variability differences between group I and II subjects remains to be clarified. However, except for borderline low values in group I subject 4 (SD = 32 ms and SDANN = 59 ms on day 2), HR variability of all normal subjects was well outside the range reported for patient populations with different disease states.[1-6] The fact that a small number of our patients with CHF have HR variability values in the normal range probably reflects persistence of vagal activity in association with reasonably good compensation.

Given the inverse correlation between HR and HR variability, differences in mean HR between different recording periods may influence the reproducibility of HR variability and should be taken into consideration when groups or individual subjects, or both, are compared. The new CV measure, which is normalized for HR, minimizes or eliminates this potentially confounding factor.

Gender and heart rate variability: This study confirms findings by Rich et al,[2] using the SDANN measure, of a lower HR variability in women than in men (Table III). However, they did not comment on their findings or provide mean HR data for men and women. Gender differences in HR variability in our study appear to largely reflect differences in HR (i.e., the lower mean HR in men), because determinations using the CV measure, which corrects for HR, were approximately equal for the 2 sexes.

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Comparison of Transthoracic and Transesophageal Echocardiography for Assessment of Left-Sided Valvular Regurgitation

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To compare transthoracic and transesophageal echocardiography in the clinical assessment of left-sided valvular regurgitation, 118 patients who underwent both transesophageal and transthoracic echocardiographic studies within a 24-hour period were included in this study. Presence or absence of aortic regurgitation was identified concordantly by both techniques in 93 patients (79%). Complete agreement between both techniques was found in 88 patients (75%). Presence or absence of mitral regurgitation was identified concordantly by both techniques in 89 patients (75%). Complete agreement in grade was found in only 74 patients (63%). Twenty-nine patients (25%) had mitral regurgitation detected by transesophageal echocardiography, but not by transthoracic echocardiography. Four of these patients (14%) had significant (2 to 3+) mitral regurgitation. Differences between transesophageal and transthoracic echocardiography do not appear to be clinically important in patients with aortic regurgitation. In mitral regurgitation, significant differences exist between these 2 techniques, with transesophageal echocardiography being much more sensitive.

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Doppler color flow echocardiography is a sensitive technique for detecting valvular regurgitation and provides a semiquantitative method of estimating severity. Previous studies using transthoracic echocardiography have demonstrated a good correlation between measurements of the color flow regurgitant jets and the angiographic severity of aortic and mitral regurgitation.[1,2] Thus, accurate criteria have been defined to assess the severity of mitral or aortic regurgitation by color flow Doppler transthoracic echocardiography. Despite the increasing use of transesophageal echocardiography, only a few studies have examined the evaluation of left-sided valvular regurgitation by this technique and compared it with that by angiography or transthoracic echocardiography.[3–5] Because both techniques are now often performed on the same patients, the purpose of the present study was to compare transthoracic and transesophageal echocardiography in both the identification and estimation of the severity of aortic and mitral regurgitation.

METHODS

Patients: In all, 138 patients who underwent both transesophageal and transthoracic echocardiographic studies within a 24-hour period without a significant intervening change in clinical status were included in this study. Twenty patients who had mitral valve prostheses (15 mechanical and 5 biological) were excluded from the study. Thus, 118 patients constituted the study group. Both echocardiographic studies were performed as part of the routine clinical evaluation of these patients. To avoid changes in hemodynamic conditions between the 2 echocardiographic studies, no intraoperative studies were included.

Indications for the echocardiographic studies were unexplained cerebrovascular ischemia in 37 patients (32%), possible aortic dissection in 11 (9%), assessment of mitral regurgitation severity in 25 (21%), evaluation for cardiac mass in 10 (8%), premitral balloon valvuloplasty in 7 (6%), evaluation of left ventricular function in 5 (4%), endocarditis in 11 (9%) and miscellaneous in 12 (11%). Written informed consent was obtained from all patients for transesophageal studies.

Echocardiographic studies: Color flow echocardiography was performed using commercially available sys-

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tems (Hewlett Packard 77020 AC or Interspec 750 CFM) with a 2.5 MHz transthoracic transducer and a 5 MHz transesophageal transducer. Transthoracic studies were performed using multiple planes, including 2-, 4- and 5-chamber views, and parasternal short- and long-axis views. Instrument settings such as color gain, depth, transmit power and color flow map were individualized to yield optimal images. For transesophageal echocardiographic studies, the mitral and aortic valves were evaluated by using the standard 4- and 5-chamber views, and the basal short axis view or slight modifications of these, or a combination. The transmit power and color flow map were carefully maintained throughout all the studies. Color flow gain was set to immediately below the level where the artifacts began to appear. All studies were recorded on a one-half inch VHS video tape for further analysis.

Color flow analysis: Tapes were carefully reviewed by 2 independent observers unaware of the transthoracic and transesophageal echocardiographic results, respectively. The degree of mitral regurgitation was assessed by both transesophageal and transthoracic studies using a 0 to 3+ scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) based on the estimated maximal regurgitant area.[6] For transthoracic studies, mitral regurgitation was considered mild (1+) when the maximal regurgitant area was <4 cm^2, moderate (2+) when the maximal regurgitant area was 4 to 8 cm^2, and severe (3+) when the maximal regurgitant area was >8 cm^2.[6] For transesophageal studies, the cutoff points for mild, moderate and severe regurgitation were 3 and 6 cm^2.[7] Aortic regurgitation was quantitated by both transesophageal and transthoracic studies based on the ratio of regurgitant jet width and left ventricular outflow tract diameter or of regurgitant jet area and aortic root area using the short-axis view. Aortic regurgitation was considered mild (1+) when the estimated ratio was $\leq$25%, moderate (2+) when the ratio was 25 to 50%, and severe (3+) when the ratio was $\geq$50%.

In 56 patients (control group), the maximal regurgitant jet area obtained by transesophageal echocardiography was traced to be compared with the subjective assessment of the severity of valvular regurgitation. The videoframe containing the maximal regurgitant jet area from any view was selected for analysis. All measurements were obtained using a commercially available echocardiographic analysis system. Only the mosaic aspect of the regurgitant areas was measured by direct planimetry. Adjacent low-velocity swirling flow was not included in the measurements.

Statistical analysis: Correlation between the semiquantitative estimation of the valvular regurgitation and the maximal regurgitant area values were obtained with the Pearson correlation coefficient.

RESULTS

A very good correlation (r = 0.85) was obtained between the visual semiquantitative estimation of the severity of regurgitation and the off-line planimetered maximal regurgitant jet area (Figure 1) in the transesophageal studies of 56 patients used as the control group.

Aortic regurgitation: Presence or absence of aortic regurgitation was identified concordantly by both techniques in 93 patients (79%) (Figure 2). Complete agreement between both techniques was found for 88 patients (75%). Transesophageal echocardiography identified 21 patients (18%) with aortic regurgitation

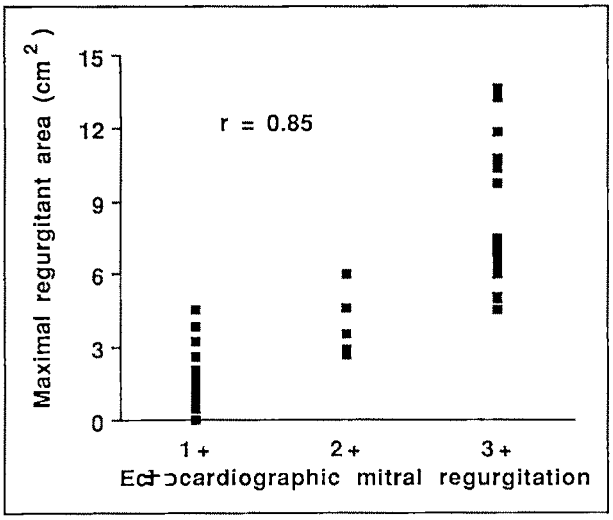

FIGURE 1. Correlation between semiquantitative visual estimation of degree of mitral regurgitation and off-line planimetered maximal regurgitant area in transesophageal studies.

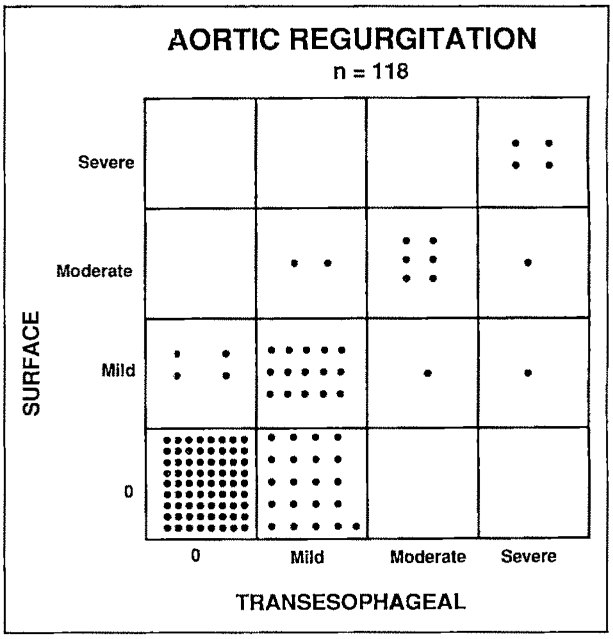

FIGURE 2. Comparison of transesophageal and transthoracic results in the evaluation of aortic regurgitation.

that was not observed with transthoracic studies. All 21 patients had 1+ aortic regurgitation by transesophageal echocardiography. Conversely, transthoracic echocardiography identified 4 patients (3%) with aortic regurgitation not observed with transesophageal echocardiography. All these patients had 1+ aortic regurgitation. Among the 30 patients with aortic regurgitation detected by both techniques, there was a difference of 1 grade in 4 patients (13%) and of 2 grades in only 1 patient (3%). In 2 of the 4 patients with a 1-grade difference, the degree of aortic regurgitation was greater with transesophageal echocardiography. One of these 2 patients had technically difficult surface echocardiograms, and the other had a vegetation that was not seen with transthoracic echocardiography. In 2 patients, the degree of aortic regurgitation was more severe by transthoracic echocardiography. One of these patients had a severely dilated and elongated aortic root that resulted in a difficult assessment of aortic regurgitation by transesophageal echocardiography due to the inability to obtain a true short-axis view. The remaining patient had associated aortic stenosis. The patient with a 2-grade difference had a technically difficult transthoracic study.

Mitral regurgitation: Presence or absence of mitral regurgitation was identified concordantly by both techniques in 89 of 118 (75%) patients (Figure 3). Complete agreement in grade was found for only 74 patients (63%). Twenty-nine patients (25%) had mitral regurgitation detected only by transesophageal echocardiography. Twenty-five (86%) of these patients had 1+, 3 patients (10%) had 2+, and 1 patient had 3+ mitral regurgitation. The patient with severe (3+) mitral regurgitation had a technically difficult surface study. Among the 63 patients with mitral regurgitation detected by both techniques, 14 (22%) had a 1-grade and 1 (2%) had a 2-grade difference. The patient with a 2-grade difference had a technically difficult surface echocardiogram. Of the 14 patients with a 1-grade difference, 9 had a greater degree of mitral regurgitation by transesophageal echocardiography and 5 by surface echocardiography. Of the latter 5 patients, 1 had mitral valve repair, 2 had associated mitral stenosis and 2 had papillary muscle dysfunction with poor left ventricular contractility. Of the 9 patients with more severe mitral regurgitation by transesophageal echocardiography, 3 had technically difficult surface studies, 3 had papillary muscle dysfunction secondary to myocardial ischemia and had poor left ventricular function, and 3 had eccentric jets secondary to flail mitral leaflet.

DISCUSSION

During the past decade, Doppler echocardiography has been established as the noninvasive method of choice for the evaluation of patients with valvular regurgitation. Pulsed, continuous-wave and, most recently, color flow Doppler have all been shown to correlate well with invasive measurements of valvular regurgitation using standard transthoracic Doppler echocardiography.[1,2,6]

Transesophageal echocardiography has been used with increasing frequency over the past years. Indications for this procedure are many and often include evaluation of patients with valvular heart disease.[8,9] Unfortunately, few data exist evaluating the accuracy of transesophageal Doppler echocardiography in the diagnosis and quantitation of valvular regurgitation. Furthermore, methods for assessing regurgitant lesions by conventional transthoracic Doppler echocardiography may not apply to transesophageal echocardiography where ultrasound attenuation is markedly reduced.[5,7]

Mitral regurgitation: The degree of mitral regurgitation was quantitated from transthoracic and transesophageal studies by the size of the regurgitant jet.[6,7] Transesophageal echocardiography appeared to be much more sensitive for the detection of mitral regurgitation. In fact, one fourth of the patients in whom mitral regurgitation was detected by transesophageal echocardiography had no evidence of regurgitation by transthoracic study. More importantly, 14% of these patients had hemodynamically significant lesions (moderate to severe mitral regurgitation). Similar results were obtained by Smith et al[5] who compared the regurgitant jet area size in transesophageal and transthoracic studies. Both quantitative and semiquantitative visual grading of mitral regurgitant jets revealed a higher grade of regurgitation by esophageal imaging.

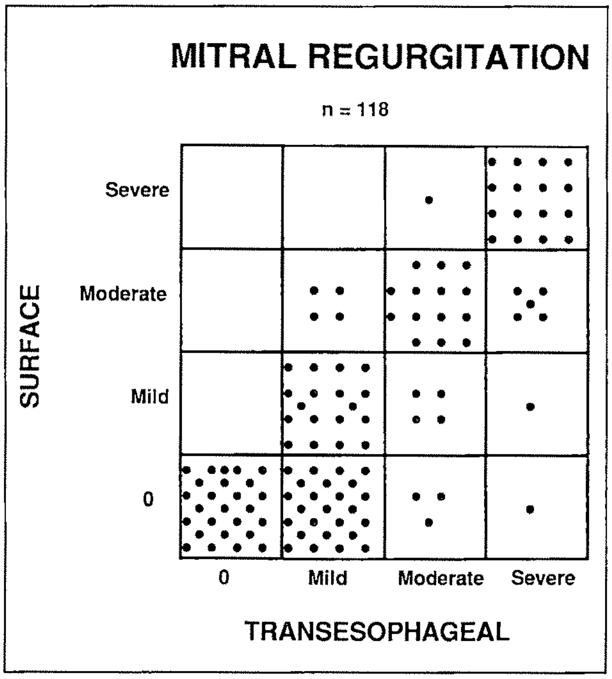

FIGURE 3. Comparison of transesophageal and transthoracic results in the evaluation of mitral regurgitation.

Aortic regurgitation: The difference between transthoracic and transesophageal studies in the detection and quantitation of aortic regurgitation was not nearly as great as that of mitral regurgitation. Transesophageal echocardiography detected aortic regurgitation not noted by transthoracic study in only 17% of patients. The fact that regurgitation was judged to be mild in all cases was also noteworthy. In addition, there were 5 patients with mild aortic regurgitation identified only by transthoracic study. Likewise, there was much closer agreement in the degree of regurgitation as estimated by both techniques. Therefore, it appears that the advantages of transesophageal echocardiography in the evaluation of the mitral valve, including unimpeded ultrasound beam and proximity to the regurgitant jet, are not present in the evaluation of aortic valve pathology. Often, there is some degree of acoustic impedance of the echoes in the left ventricular outflow tract beyond the calcified aortic valve. It can be difficult to evaluate the full course of the aortic regurgitant jet using 1-plane transducers.

Conclusion: Differences exist in the quantitation of left-sided valvular regurgitation as measured by transthoracic and transesophageal echocardiography, and estimated semiquantitatively. These differences do not appear to be clinically important in patients with aortic regurgitation, particularly when a high-quality transthoracic study is performed. However, in mitral regurgitation, significant differences exist, with transesophageal echocardiography being much more sensitive. Quantitative color flow Doppler studies[5] have confirmed these findings. Transesophageal echocardiography should be strongly recommended for the evaluation of suspected mitral regurgitation, particularly when important clinical decisions may be based on the outcome of the study.

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Pulmonary Valve-Moderator Band Distance and Association with Development of Double-Chambered Right Ventricle

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Double-chambered right ventricle (DCRV), a form of right ventricular outflow obstruction that sometimes accompanies a ventricular septal defect (VSD), is associated with superior and rightward displacement of the septal insertion of the moderator band. It was hypothesized that this superior displacement is present and identifiable by echocardiography in patients with a VSD even before right ventricular outflow tract obstruction develops. Eight patients who had a previous echocardiographic study showing a VSD alone were echocardiographically diagnosed as having DCRV. Their initial echocardiographic studies were reviewed, and superior displacement of the moderator band was quantified by measuring the distance between the pulmonary valve and moderator band, normalized to tricuspid anulus diameter. These measurements were compared with those from the initial studies of the following 3 other groups: (1) an age-matched group of 10 patients with no structural heart disease; (2) an age-matched group of 10 patients with a VSD who did not develop DCRV; and (3) a group (not age-matched) of 10 patients with VSD and DCRV in whom subpulmonary obstruction was present on the initial study. The 8 patients who eventually developed subpulmonary obstruction had significant superior displacement of the moderator band at the time of their initial echocardiogram compared with that of the 2 age-matched control groups (p <0.01). In contrast, there was no significant difference in moderator band displacement between these patients and the 10 with DCRV who already had right ventricular outflow obstruction at their initial study (p = not significant).

Superior displacement of the moderator band is quantifiable by 2-dimensional echocardiography and may help to predict which infants with a VSD are at risk to develop subpulmonary obstruction.

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Double-chambered right ventricle (DCRV) is a form of right ventricular outflow obstruction characterized by muscular narrowing that partitions the right ventricle into an inflow and outflow chamber. It is anatomically distinct from tetralogy of Fallot, where right ventricular obstruction is the result of anterior malalignment of the infundibular septum. For more than a century, this type of muscular subdivision of the right ventricle has been recognized as a pathologic entity.[1,2] However, it was not until the early 1960s that its natural history and distinct laboratory findings were first described.[3–5] Since then, the pathologic, angiographic and echocardiographic features of DCRV, as well as its surgical repair and long-term follow-up, have been reported.[3–13]

DCRV is an acquired form of outflow obstruction that often develops in association with a ventricular septal defect (VSD).[6,13] This conclusion is supported by the following 3 observations: (1) Most cases of DCRV are diagnosed after the neonatal period.[4,6,7] (2) Progression of right ventricular outflow obstruction in unrepaired DCRV has been well-documented by catheterization.[4,5,7,12,14] (3) DCRV is associated with a VSD at the time of diagnosis in 80 to 90% of cases.[3,9] The actual incidence of development of DCRV in patients with a VSD is still unclear. During the past 10 years, approximately 3% of patients at our institution diagnosed with a membranous VSD have also had DCRV, and a recent surgical report noted a 10 to 11% incidence of DCRV in all patients undergoing surgery for a VSD.[12] Consequently, it would be useful to know what anatomic features recognizable by echocardiography may predict which infants with a VSD are likely to

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develop DCRV. The purpose of this study was to identify such features.

METHODS

Patient selection: All patients diagnosed with DCRV and VSD between July 1986 and July 1989 at our institution were identified by a search of the computerized cardiology database. The diagnosis of DCRV was based on the following echocardiographic criteria: (1) muscular subpulmonary obstruction without evidence of anterior deviation of the infundibular septum[10]; and (2) a Doppler maximal instantaneous gradient of ≥20 mm Hg at the site of anatomic narrowing. Patients with other congenital heart defects (including tetralogy of Fallot, double-outlet right ventricle and aortic stenosis) were excluded. The patients were divided into the following 2 groups: those who had a prior echocardiographic examination demonstrating only a VSD with no significant right ventricular outflow gradient (preDCRV patients); and those who already had a right ventricular outflow gradient >20 mm Hg at the initial echocardiogram (DCRV patients).

Two control groups matched for age with the preDCRV group were randomly chosen from all patients who had an echocardiogram between July 1986 and July 1989 and were grouped as follows: (1) 10 with no structural heart disease (normal patients); and (2) 10 with a membranous VSD at the initial study who did not develop right ventricular outflow obstruction (VSD patients) during a follow-up period comparable in length to that of the preDCRV patients.

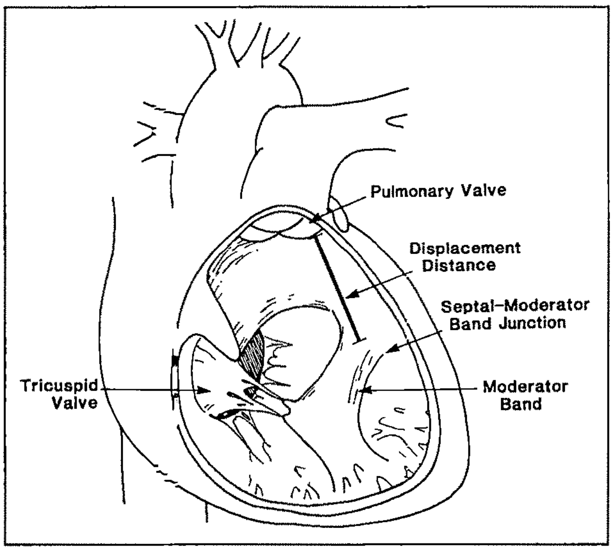


FIGURE 1. Interior of right ventricle with free wall removed. Distance between midpoint of septal insertion of moderator band and pulmonary valve anulus represents displacement distance. Moderator band is thickened and superiorly displaced to illustrate changes that might be seen in double-chambered right ventricle.

Design of measurements: Based on a review of the literature we hypothesized that the most likely mechanism for subpulmonary obstruction in DCRV was superior displacement of the moderator band.[8-12,14,15] To quantify this we measured the distance between the pulmonary valve anulus and the septal insertion of the moderator band (displacement distance; Figure 1) by echocardiography and from pathologic specimens. In order to obtain comparisons between patients of different body and heart sizes, the displacement distance was normalized (i.e., indexed) by dividing it by the tricuspid anulus diameter (displacement index).

Echocardiographic studies: All echocardiograms were performed with a Hewlett-Packard 77020 or Acuson cardiac imager equipped with a 5 MHz short- or medium-focus transducer. A complete examination was performed in each case, including subxiphoid, apical, parasternal and suprasternal notch views. Sedation with chloral hydrate was used when necessary. The examinations were recorded on one-half inch videocassette tape. The videotape of each patient's echocardiogram was reviewed, and selected still frames were identified. Hard copies were obtained using a Mitsubishi thermal printer, and measurements were made directly on the printed image.

Displacement distance was measured at end-diastole in the subxiphoid short-axis view from the midpoint of the insertion of the moderator band in the ventricular septum to the pulmonary valve anulus (Figure 2). The end-diastolic frame was taken as the frame immediately before ventricular contraction occurred. Tricuspid anulus diameter was measured in the apical 4-chamber view at early to mid-diastole when the inflow dimensions were greatest. Measurements of displacement distance and tricuspid valve diameter were obtained independently by 2 observers. VSD diameter was measured at end-diastole in the parasternal long- and short-axis views (1 measurement in each plane), and an average value was obtained. Doppler velocity across the right ventricular outflow tract (right ventricular outflow velocity) was recorded. Maximal instantaneous gradient was estimated using the modified Bernoulli equation (gradient = $4 \times [\text{velocity}]^2$).[16]

Pathologic studies: Each measurement was also performed on selected pathologic specimens in the cardiac registry collection at our institution. Specimens were obtained from the following 3 groups: (1) patients with a structurally normal heart ("normal" specimens); (2) patients with a membranous VSD alone (VSD specimens); and (3) patients with DCRV (DCRV specimens). In each of the first 2 groups, 15 specimens were randomly selected for examination. In the third group, all specimens were examined, although only 5 met the criteria of DCRV and had no other congenital cardiac lesions.

Measurements were made directly on each specimen. The anatomic sites defining the end points of the line to be measured were identified. The end of a straight dissection probe was placed at 1 site, and the location of the other site was marked on the probe with a dissection clamp. Each measurement was repeated 3 times, and the mean value was used for data analysis. The measurements were obtained in anatomic planes comparable to the relevant echocardiographic planes. Measurements were indexed for tricuspid anulus diameter.

Statistics: Data are presented as mean value ± standard deviation for each group of measurements. In both the echocardiographic and pathologic studies, normalized measurements were compared among groups using 1-way analysis of variance. Statistical significance of the differences between groups was assessed by the Student-Newman-Keuls test for multiple subject group comparison. Interobserver variability was assessed using a paired *t* test. For all tests, a p value ≤0.05 was considered significant.

RESULTS

Echocardiography: Eighteen patients were identified who had the echocardiographic diagnosis of DCRV and VSD. Of these, 8 patients had a previous echocardiogram showing no right ventricular outflow obstruction (preDCRV group). Mean age of these patients at the time of initial echocardiogram was 0.7 ± 0.4 months. The remaining 10 patients already had right ventricular outflow obstruction on their initial study (DCRV group). Mean age at the time of study

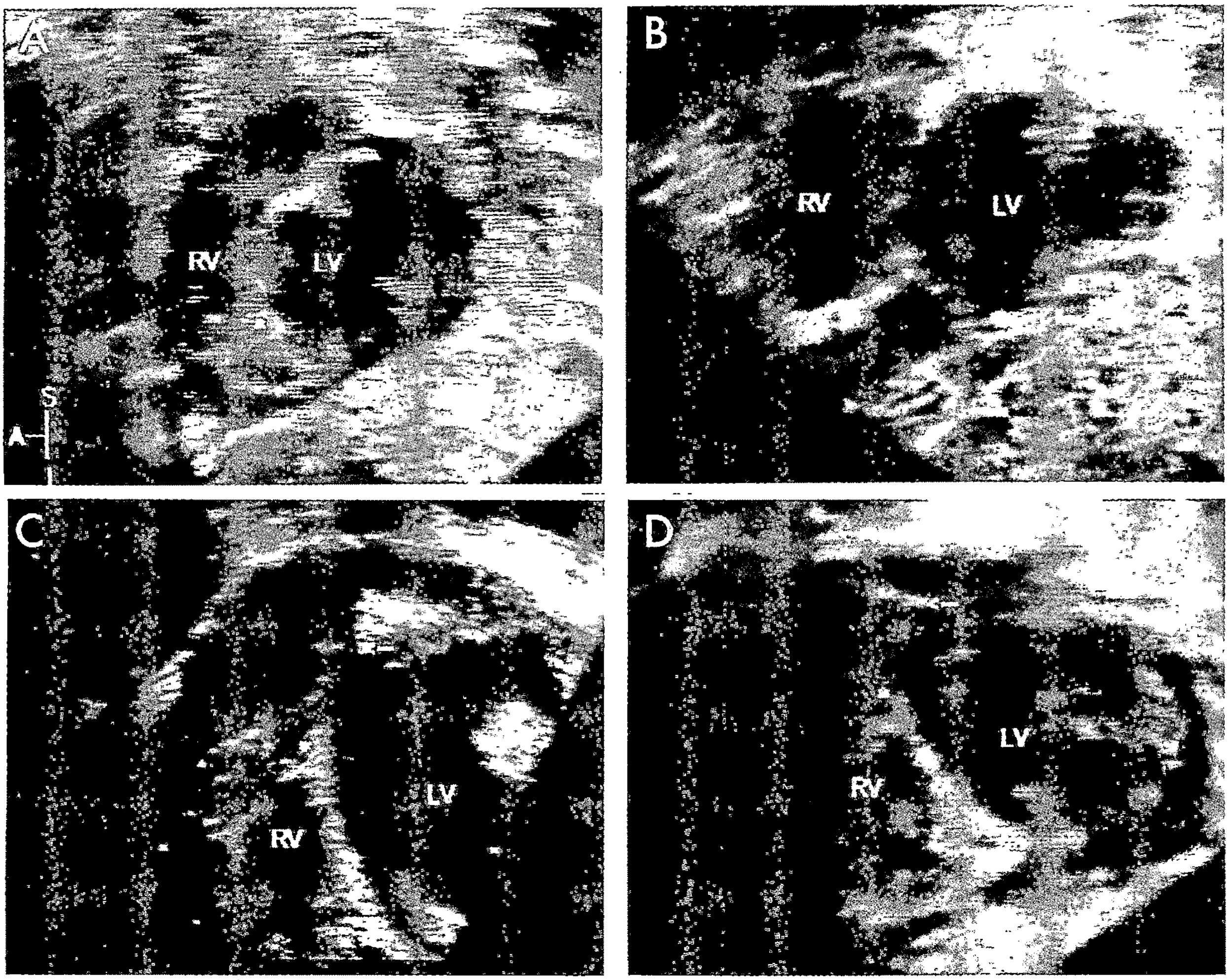


FIGURE 2. Still frames obtained from 2-dimensional echocardiograms of normal patient *(A)*, ventricular septal defect (VSD) patient *(B)*, double-chambered right ventricle (DCRV) patient *(C)*, and preDCRV patient *(D)*. Echocardiograms were obtained in subxiphoid short-axis view with leftward angulation of transducer. Because of this angulation, VSD is not visible in *B* through *D*. Displacement distance is separation between moderator/septal band junction *(asterisks)* and pulmonary valve *(arrows)*. Moderator band appears superiorly displaced in both preDCRV and DCRV patients, but not in normal or VSD patients. A = anterior; I = inferior; LV = left ventricle; preDCRV = ventricular septal defect with no significant right ventricular outflow gradient; RV = right ventricle; S = superior.

TABLE I Echocardiographic Measurements

	Groups			
	Normal	VSD	PreDCRV	DCRV
Displacement distance (mm)				
Observer no. 1	17.3 ± 2.9	19.1 ± 3.9	9.9 ± 2.5*	14.2 ± 3.6†
Observer no. 2	18.3 ± 2.9‡	18.4 ± 3.1	11.1 ± 3.8*	16.9 ± 3.3§
TVA (mm)				
Observer no. 1	12.3 ± 1.8	12.2 ± 2.7	12.9 ± 1.6	18.4 ± 2.8‖
Observer no. 2	11.5 ± 1.5	13.5 ± 3.1‡	14.1 ± 3.3	18.9 ± 5.6‖
Displacement index				
Observer no. 1	1.4 ± 0.14	1.6 ± 0.28	0.76 ± 0.13*	0.78 ± 0.19*
Observer no. 2	1.6 ± 0.18‡	1.4 ± 0.33	0.79 ± 0.22*	0.90 ± 0.18*

Intraobserver comparisons: *p <0.01 vs normal, VSD group; †p <0.05 vs VSD, preDCRV group; §p <0.01 vs preDCRV group; ‖p <0.01 vs normal, VSD and preDCRV groups.
Interobserver comparisons: ‡p <0.05, observer no. 1 vs no. 2.
DCRV = double-chambered right ventricle; PreDCRV = ventricular septal defect with no significant right ventricular outflow gradient; TVA = tricuspid valve anulus; VSD = ventricular septal defect.

was 17.7 ± 9.[illegible] months. Mean age at the time of initial study was 0.9 ± 0.5 months for the normal patients, and 1.0 ± 0.9 months for the VSD patients. There was no significant difference in mean ages between the preDCRV, normal and VSD groups. However, mean age of the DCRV group was significantly greater than those of the other 3 groups (p <0.01). Length of follow-up did not differ significantly between the preDCRV and VSD groups (13.2 ± 9.6 vs 15.1 ± 7.2 months; p >0.05).

Mean displacement index was 0.76 ± 0.13 for the preDCRV patients, 0.78 ± 0.19 for the DCRV patients, 1.4 ± 0.14 for the normal patients, and 1.6 ± 0.28 for the VSD patients (Figure 3). Displacement index did not differ significantly between the normal and VSD patients (p >0.05), nor between the DCRV and preDCRV patients (p >0.05). However, displacement index was significantly smaller in the DCRV and preDCRV patients than in either the VSD or normal patients (p <0.01). Moderator band displacement in the DCRV and preDCRV patients was remarkably consistent. All preDCRV and 9 of 10 DCRV patients had a displacement index <1.0. In contrast, all normal and VSD patients had a displacement index >1.15. Interobserver comparisons demonstrated a significant difference in displacement index for normal patients, but not for those from the other 3 groups (Table I). In addition, the same relation in displacement indexes among the 4 patient groups was found by each observer.

The subpulmonary maximal instantaneous gradient did not differ significantly between the normal and VSD groups (2.2 ± 2.0 vs 3.9 ± 2.9 mm Hg; p >0.05) at the time of initial study (Table II). In comparison, the preDCRV patients had a slightly greater subpulmonary maximal instantaneous gradient of 7.4 ± 3.2 mm Hg (p <0.01 vs normal group and p <0.05 vs VSD group). Mean VSD diameter did not differ significantly between the preDCRV and VSD groups, but was significantly greater in the older DCRV patients.

Pathology: Mean age at death was 8.4 ± 5.6 years (range 0.8 to 18) for the 15 patients with structurally normal hearts, 7.2 ± 5.7 years (range 1.2 to 18.1) for the 15 patients with a VSD, and 24.8 ± 33.9 years

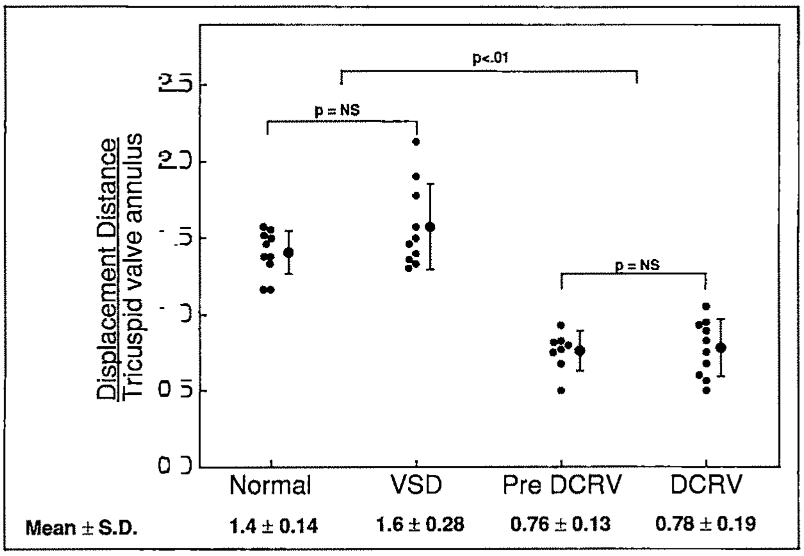


FIGURE 3. Echocardiographic result (observer no. 1). Displacement distance is normalized to tricuspid anulus diameter for all 4 groups. Mean values ± standard deviation (S.D.) are displayed below each category. Displacement distance is significantly less in the PreDCRV and DCRV groups than in the normal and VSD groups. NS = not significant; other abbreviations as in Figure 2.

TABLE II Additional Echocardiographic Data

	Groups			
	Normal	VSD	PreDCRV	DCRV
Mean VSD diameter (mm)	—	5.0 ± 1.5	4.6 ± 1.4	8.3 ± 2.2*
Doppler measurements				
VSD gradient (mm Hg)	—	10.2 ± 8.5	4.1 ± 3.4	15.3 ± 15.2†
RV outflow gradient (mm Hg)	2.2 ± 2.0	3.9 ± 2.9	7.4 ± 3.2‡	55.7 ± 13.1§

*p <0.01 vs VSD and preDCRV groups; †p <0.05 vs preDCRV group; ‡p <0.01 vs normal and VSD groups; §p <0.05 vs normal, VSD and preDCRV groups.
RV = right ventricular; other abbreviations as in Table I.

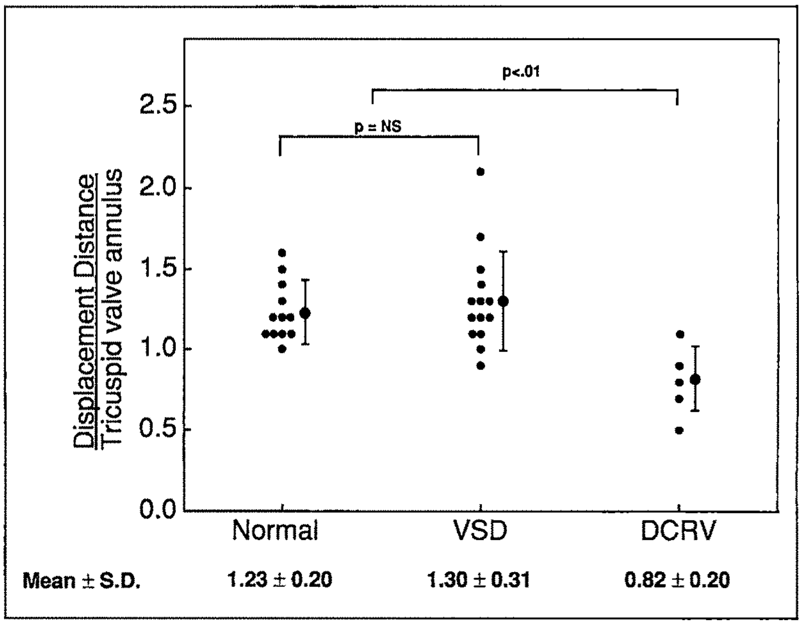
(range 0.5 to 84) for the 5 patients with DCRV. Mean displacement index was 1.23 ± 0.20 for the normal patients, 1.30 ± 0.31 for the VSD patients, and 0.82 ± 0.20 for the DCRV patients (Figure 4). There was no significant difference in displacement index between the normal and VSD patients (p >0.10). However, the displacement index was significantly smaller in the DCRV patients (p <0.01).

DISCUSSION

Two major findings emerged from this study. First, the moderator band was found to be superiorly displaced (even at the initial echocardiographic study) in those infants with a VSD who eventually developed DCRV. No displacement of the moderator band was seen in age-matched patients with a VSD who did not develop DCRV. This suggests that the anatomic substrate for DCRV exists before the development of a pressure gradient. Possible mechanisms for development of muscular obstruction include: (1) hypertrophy of the parietal, moderator and septal bands causing progressive stenosis of the proximal os infundibuli; and (2) the size of the os infundibuli may not change significantly with somatic growth, resulting in a progressive mismatch between the cross-sectional area of the os infundibuli and the cardiac output. The contribution of a left-to-right shunt across the VSD in the genesis of the subpulmonary obstruction remains to be determined. Second, the superior displacement of the moderator band can be detected by echocardiography. Virtually all DCRV and preDCRV patients had a displacement index <1.0. Displacement distance can be obtained by echocardiography using standard (or slightly angled) subxiphoid views. Tricuspid anulus diameter is readily obtained from the apical 4-chamber view. Although there was a small amount of interobserver variability in individual measurements, both observers found the same relation in displacement index among the 4 study groups. Displacement index values were further corroborated by examination and measurement of pathologic specimens.

In addition to displacement distance, other measurements were attempted to quantify the anatomic features of DCRV, such as os infundibuli diameter and parietal band length. However, we found these dimensions difficult to measure accurately and consistently by echocardiography. Among all echocardiographic measurements examined, displacement distance was the

FIGURE 4. Pathologic results. Displacement distance is normalized to tricuspid anulus diameter for all 3 groups of specimens. Mean values ± standard deviation (S.D.) are displayed below each category. Displacement distance is significantly less in DCRV than in normal and VSD specimens. Abbreviations as in Figures 2 and 3.



easiest to obtain and the most reproducible. This distance was divided by tricuspid anulus diameter to normalize for differences between patients in right ventricular volume. Tricuspid anulus diameter has previously been shown to correlate closely with right ventricular volume.[17]

This study, our own recent surgical experience and much of the recent literature[8–10,12,14–15] support the hypothesis that DCRV is due to superior displacement and hypertrophy of the moderator band. However, it should be noted that there is still debate regarding the pathologic anatomy of DCRV. Restivo et al[18] reported that there are probably several different types of DCRV, not all of which have an "anomalous muscle bundle." Other authors have questioned whether the anomalous muscle bundle seen by echocardiography and angiography is indeed a hypertrophied and displaced moderator band.[19] Whereas superior displacement of the moderator band suggests an increased risk for development of subpulmonary obstruction, the absence of this finding does not exclude the possibility of development of DCRV by some other mechanism. Moreover, until a large scale prospective study has been performed we cannot determine the sensitivity and specificity of this finding.

In conclusion, the echocardiographic finding of a superiorly displaced moderator band in a neonate with a VSD implies increased risk for the development of subpulmonary obstruction. In particular, a displacement index of <1.0 should be considered significant, and right ventricular outflow tract obstruction should be anticipated.

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MISCELLANEOUS

Acute and Long-Term Effects of Nifedipine on Pulmonary and Systemic Hemodynamics in Patients with Pulmonary Hypertension Associated with Diffuse Systemic Sclerosis, the CREST Syndrome and Mixed Connective Tissue Disease

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Ten patients with pulmonary hypertension associated with diffuse systemic sclerosis (1 patient), the CREST syndrome (calcinosis cutis, Reynaud's phenomenon, esophageal dysmotility, sclerodactyl, telangiectasia) (6 patients) and mixed connective tissue disease (3 patients) were studied to assess the effect of oral nifedipine on pulmonary and systemic hemodynamics. Each patient underwent right-sided cardiac catheterization just before nifedipine administration. Thereafter, oral nifedipine was administered in 10 mg increments every 90 minutes until pulmonary vascular resistance normalized or a total dose of 30 mg was achieved. Hemodynamic measurements were obtained at 30-minute intervals for 3 hours, then hourly for 9 hours (acute study). Hemodynamic studies were repeated 3 to 6 months after the initial catheterization with the minimum dose of oral nifedipine (administered every 8 hours) required to achieve maximal reduction of pulmonary vascular resistance in the acute study (long-term study). In the acute study, oral nifedipine produced a significant decrease in mean pulmonary vascular resistance, from 6.3 ± 3.8 to 4.3 ± 3.6 U ($p < 0.001$). Similar changes in pulmonary vascular resistance were noted in the long-term study ($n = 6$). The results indicate that oral nifedipine is capable of producing an acute and sustained reduction in pulmonary vascular resistance in patients with pulmonary hypertension associated with diffuse systemic sclerosis, the CREST syndrome and mixed connective tissue disease.

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Pulmonary hypertension is commonly present in patients with the CREST variant of systemic sclerosis (calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia).[1-3] It is encountered less frequently in patients with diffuse systemic sclerosis and mixed connective tissue disease.[1-4] The severity of pulmonary hypertension in these connective tissue diseases is variable, ranging from mild to severe.[1-21] Pulmonary hypertension may result from pulmonary fibrosis, or more often from proliferative vascular disease predominantly involving small and medium-sized pulmonary arteries.[1-23] Speculation exists that vasospasm may precede, and perhaps accompany, the pulmonary vascular lesions.[24-31] If true, then drugs that relax vascular smooth muscle (e.g. nifedipine) may reduce pulmonary vascular resistance in afflicted patients. This study assesses the effect of nifedipine on pulmonary and systemic hemodynamics in patients with pulmonary hypertension associated with diffuse systemic sclerosis, the CREST syndrome and mixed connective tissue disease.

METHODS

Patient selection: Patients with pulmonary hypertension documented by right-sided cardiac catheterization who had clinical ± serologic evidence of diffuse systemic sclerosis, the CREST syndrome or mixed connective tissue disease were considered eligible for the study. Diffuse systemic sclerosis and the CREST syndrome were diagnosed in accordance with American Rheumatism Association criteria.[32] Mixed connective

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TABLE I Patient Characteristics

Pt. No.	Age (yr) & Sex	Connective Tissue Disease	Serologic Status	Cardiopulmonary Symptom(s)	Reynaud's Phenomenom
1	F/[illegible]5	CREST syndrome	Anticentromere antibodies present	Dyspnea	+
2	M/[illegible]2	CREST syndrome	Anticentromere antibodies present	Dyspnea	+
3	F/[illegible]	Mixed connective tissue disease	Antibodies to ribonucleoprotein present	Dyspnea, lassitude	+
4	F/[illegible]5	Mixed connective tissue disease	Antibodies to ribonucleoprotein present	Dyspnea	+
5	M/[illegible]7	Diffuse systemic sclerosis	Seronegative	Dyspnea	+
6	M/[illegible]8	CREST syndrome	Seronegative	Dyspnea, lassitude	+
7	M/[illegible]0	CREST syndrome	Seronegative	Dyspnea	+
8	F/[illegible]6	Mixed connective tissue disease	Antibodies to ribonucleoprotein present	Dyspnea	+
9	M/[illegible]5	CREST syndrome	Anticentromere antibodies present	Dyspnea	+
10	M/[illegible]3	CREST syndrome	Seronegative	Dyspnea	+

CREST = calcinosis cutis, Reynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia.

tissue disease was diagnosed in accordance with the criteria of Porter et al.[33] Pulmonary hypertension was defined as elevated pulmonary vascular resistance (>1.6 U). Before consideration for entry into the study, a medical history, complete physical examination, electrocardiography at rest, chest x-ray, echocardiography (M-mode, 2-dimensional, Doppler), pulmonary function tests (arterial blood gases, spirometry, lung volumes, diffusing capacity) and right-sided cardiac catheterization were performed in each patient. Patients with evidence of pulmonary fibrosis on chest x-ray, obstructive lung disease, left ventricular failure, any form of organic heart disease unrelated to the connective tissue disease, and any acute illness, and patients receiving drugs that might influence pulmonary or systemic hemodynamics were excluded from the study. Patients entering the study who were receiving immunosuppressive therapy continued to receive such therapy for the duration of the study.

Protocol: Right-sided cardiac catheterization was performed in the cardiac catheterization laboratory using an end-hole, balloon-tipped, flow-directed, pulmonary artery catheter. After placement of the catheter, patients were transferred to the coronary care unit for follow-up hemodynamic studies.

After an 8-hour period of equilibration, baseline hemodynamic measurements were obtained. Mean blood pressure (cuff) was calculated by adding one-third of the pulse pressure to the diastolic blood pressure. Cardiac output was measured using the thermodilution method. Mean pulmonary artery, mean pulmonary capillary wedge and mean right atrial pressures were directly measured. Systemic and pulmonary vascular resistance values were calculated using standard formulas. The maximum variation in pulmonary vascular resistance during the equilibration period was 6%.

After baseline hemodynamic measurements, 10 mg of nifedipine was administered orally at 90-minute intervals up to a total dose of 30 mg, or lower, if pulmonary vascular resistance normalized. Pulmonary and systemic hemodynamic data were recorded at 30-minute intervals for 3 hours, then hourly for 9 additional hours (acute study). The pulmonary artery catheter was then removed. Patients were treated chronically (at 8-hour intervals) with the lowest dose of oral nifedipine that provided the maximum reduction in pulmonary vascular resistance.

Three to 6 months (mean 4.5) after the initial right-sided cardiac catheterization, patients underwent a repeat catheterization (long-term study). Drug regimens were identical to those in place at the time of baseline hemodynamic measurements except for the addition of oral nifedipine. Repeat right-sided cardiac catheterizations were performed 3 to 4 hours after the administration of the patient's usual dose of oral nifedipine.

Statistical methods: The Wilcoxon rank sum test was used to analyze paired comparisons. A Bonferroni correction was applied because there were 2 paired comparisons for each variable. Thus, a p value <0.025 was required to achieve a significance level of >95%.

RESULTS

Patient characteristics: Twenty-four patients were initially considered for entry into the study. Four were excluded on the basis of data derived from the medical history, physical examination, electrocardiogram at rest, chest x-ray, echocardiogram or pulmonary function tests. Eighteen patients underwent right-sided cardiac catheterization. Of these, 10 had elevated pulmonary vascular resistance and entered the study. Individual data concerning age, sex, type of connective tissue disease, serologic status, cardiopulmonary symptoms and the presence or absence of Raynaud's phenomenon are listed in Table I. Of the 10 patients participating in the acute study, 6 volunteered to participate in the long-term study. Three patients declined repeat right-sided catheterization and 1 died of pneumonia 3 months after the initial cardiac catheterization.

Effects on pulmonary and systemic hemodynamics — acute study: Table II lists the individual and mean

TABLE II Acute and Long-Term Hemodynamic Responses to Oral Nifedipine Therapy: Individual and Mean Data

	Mean Blood Pressure (mm Hg)				Systemic Vascular Resistance (units)				Cardiac Output (liters/min)				Mean Pulmonary Artery Pressure (mm Hg)			
	Acute		Long-Term		Acute		Long-Term		Acute		Long-Term		Acute		Long-Term	
Pts.	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	91	88	91	87	15.5	14.6	15.5	14.0	5.6	5.8	5.6	5.3	28	16	28	17
2	118	105	118	103	22.9	18.5	22.9	18.4	4.8	5.4	4.8	5.3	58	46	58	44
3	96	91	96	94	17.5	15.1	17.5	15.7	5.4	5.8	5.4	5.8	31	18	31	19
4	103	96	103	96	18.2	16.6	18.2	15.2	5.0	5.3	5.0	5.8	62	48	62	46
5	115	109	115	107	20.0	18.1	20.0	18.7	5.6	5.9	5.6	6.0	27	16	27	15
6	98	95	98	96	19.1	17.4	19.1	16.4	4.6	5.0	4.6	5.2	70	54	70	58
7	96	94	—	—	16.0	15.4	—	—	5.7	5.9	—	—	36	22	—	—
8	93	90	—	—	17.2	15.7	—	—	5.5	6.0	—	—	26	16	—	—
9	100	95	—	—	17.8	15.5	—	—	5.5	6.0	—	—	26	16	—	—
10	96	93	—	—	17.8	17.3	—	—	4.9	4.9	—	—	58	60	—	—
Mean	101	96*	103	97	18.2	16.4†	18.8	16.4*	5.3	5.6†	5.2	5.7†	42	31‡	46·	33‡
±1SD	±9	±7	±11	±7	±2.1	±1.3	±2.5	±1.8	±0.4	±0.4	±0.4	±0.3	±18	±18	±19	±18

*p <0.01; †p <0.001; ‡p <0.00005; §p <0.025 compared with analagous hemodynamic variable before nifedipine

Acute nifedipine dose = cumulative dose used in acute study; Post = hemodynamic variable after nifedipine administration in acute and long-term studies; Pre = hemodynamic variable before nifedipine administration; SD = standard deviation.

TABLE II (continued)

	Mean Pulmonary Capillary Wedge Pressure (mm Hg)				Pulmonary Vascular Resistance (units)				Mean Right Atrial Pressure (mm Hg) Output (liters/min)					
	Acute		Long-Term		Acute		Long-Term		Acute		Long-Term		Nifedipine Dosage (mg)	
Pts.	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Acute	Long-Term
1	10	9	10	8	3.0	1.2	3.0	1.1	4	3	4	3	10	10 q 8 hrs
2	12	8	12	10	9.6	7.0	9.6	6.4	8	5	8	5	30	30 q 8 hrs
3	8	8	8	8	4.2	1.7	4.2	1.9	3	3	3	3	20	20 q 8 hrs
4	10	9	10	8	10.4	7.7	10.4	6.6	12	8	12	8	30	30 q 8 hrs
5	12	10	12	9	2.7	1.0	2.7	1.0	3	2	3	2	10	10 q 8 hrs
6	12	10	12	11	12.6	8.8	12.6	8.9	10	8	10	9	30	30 q 8 hrs
7	10	8	—	—	4.6	2.4	—	—	5	3	—	—	20	—
8	12	11	—	—	3.4	1.2	—	—	2	2	—	—	10	—
9	11	9	—	—	2.7	1.2	—	—	2	2	—	—	10	—
10	10	8	—	—	9.8	10.6	—	—	9	8	—	—	30	—
Mean	11	9†	11	9§	6.3	4.3†	7.1	4.3‡	6	4*	7	5	—	—
±1SD	±1	±1	±2	±1	±2.7	±3.8	±4.3	±3.4	±4	±3	±4	±3	—	—

hemodynamic data before and after oral nifedipine administration and the cumulative nifedipine dosages. Eight of the 10 patients studied experienced a subjective improvement in dyspnea after nifedipine administration. The percent decrease in pulmonary vascular resistance produced by nifedipine was greater than the percent decrease in systemic vascular resistance (Figure 1A).

Effects on pulmonary and systemic hemodynamics — long-term study: Table II shows the individual and mean data before nifedipine administration and 3 to 6 months after the initiation of nifedipine. All 6 patients studied experienced a long-term subjective improvement in dyspnea on nifedipine. The percent decrease in pulmonary vascular resistance was greater than that in systemic vascular resistance (Figure 1B).

DISCUSSION

Speculation exists that pulmonary vasoconstriction may contribute to the development of pulmonary hypertension in patients with diffuse systemic sclerosis and the CREST syndrome. Morgan et al[24] reported a significant decrease in pulmonary vascular resistance in 7 patients with systemic sclerosis, but not in 8 patients with primary pulmonary hypertension.[24] Case reports have documented acute elevation of pulmonary vascular resistance associated with episodes of Raynaud's phenomenon.[25,26] In contrast, Shuck et al[27] observed no significant change in pulmonary vascular resistance during episodes of Raynaud's phenomenon in 8 patients with diffuse systemic sclerosis or the CREST syndrome. Thus, pulmonary vasoconstriction appears to occur in some but not all patients with these disorders.

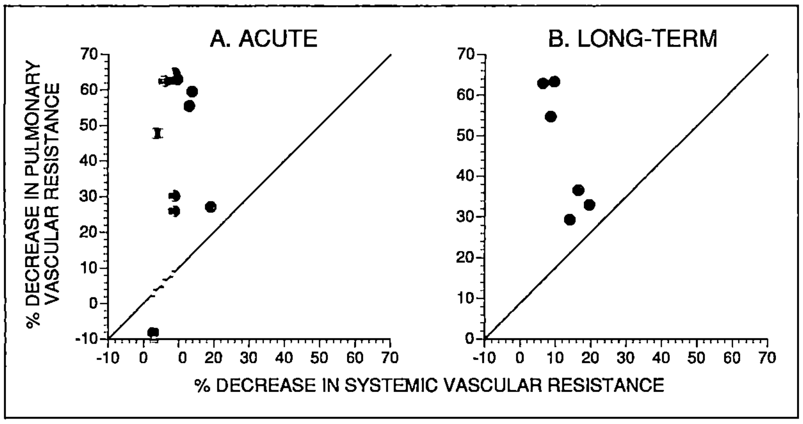

FIGURE 1. ***A.*, comparative percent changes in pulmonary and systemic vascular resistance — acute study. The percent decrease in pulmonary vascular resistance was greater than that in systemic vascular resistance after nifedipine therapy. *B.*, comparative percent changes in pulmonary and systemic vascular resistance — long-term study. The percent decrease in pulmonary vascular resistance was greater than that in systemic vascular resistance after nifedipine therapy.**

Whether pulmonary vasoconstriction in such patients predisposes to the development of the proliferative pulmonary vascular lesions noted in systemic sclerosis remains uncertain. Information is lacking concerning the role of pulmonary vasoconstriction in the development of pulmonary hypertension in patients with mixed connective tissue disease.

The presence of pulmonary vasoconstriction as a contributing factor to the development of pulmonary hypertension in diffuse systemic sclerosis and the CREST syndrome suggests that drugs that relax vascular smooth muscle such as nifedipine may be useful in reducing pulmonary vascular resistance in such persons. Glikson et al[23] reported a reduction in pulmonary vascular resistance in a 62-year-old woman with severe pulmonary hypertension associated with the CREST syndrome using a single 15 mg oral dose of nifedipine. Ocken et al[29] reported a decrease in pulmonary vascular resistance after oral administration of 20 mg of nifedipine in a 52-year-old man with severe pulmonary hypertension associated with systemic sclerosis (type unspecified). Most recently, Sfikakis et al[30] reported a significant acute decrease in mean pulmonary vascular resistance in 10 patients with systemic sclerosis (type unspecified) and borderline pulmonary hypertension after oral administration of 10 mg of nifedipine. However, Fudman and Kelling Jr.[31] reported the development of tolerance to nifedipine within 12 hours after an initial decrease in pulmonary vascular resistance in a 64-year-old woman with systemic sclerosis and severe pulmonary hypertension. There are no reports on the efficacy of nifedipine in patients with pulmonary hypertension associated with mixed connective tissue disease.

The results of this study indicate that oral nifedipine is capable of producing an acute and sustained decrease in pulmonary vascular resistance in certain patients with pulmonary hypertension associated with diffuse systemic sclerosis, the CREST syndrome and mixed connective tissue disease. The high frequency of response to nifedipine noted in this study is probably attributable to the fact that 6 of the 10 patients studied had mild to moderate pulmonary hypertension. We postulate that the pulmonary vasoconstrictive response in such patients is preserved to a greater extent than in those with severe pulmonary hypertension. Nevertheless, 3 of the 4 patients with severe pulmonary hypertension experienced a decrease in pulmonary vascular resistance (up to 40%) after nifedipine therapy. Thus, a trial of nifedipine therapy should not be excluded merely because pulmonary hypertension is advanced. Pulmonary vascular resistance decreased in response to nifedipine therapy to a greater extent than systemic vascular resistance. Whether this implies a higher degree of vasoreactivity in the pulmonary arterial bed is uncertain. The clinical significance of our findings is uncertain. The effect of nifedipine on quantifiable exercise tolerance, survival and gas exchange was not assessed. Whether reduction of pulmonary vascular resistance early in the course of diffuse systemic sclerosis, the CREST syndrome or mixed connective tissue disease prevents development of the characteristic pulmonary vascular abnormalities or retards the eventual progression of pulmonary hypertension is unknown.

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Echocardiographic Assessment of Left Ventricular Function and Wall Motion at High Altitude in Normal Subjects

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To understand the effects of high-altitude hypoxia on cardiac function and the change in cardiac function during high-altitude acclimatization, precise studies were first performed at >5,000 m of altitude in Himalaya by 2-dimensional echocardiography. In addition to examining well-known indexes of cardiac function, the centerline method was used to assess regional wall motion, which has not been examined under conditions of high-altitude hypoxia. The subjects were 11 climbing members (aged 21 to 43 years) of the Kyoto University Medical Research Expedition of Xixabangma (8,027 m) in 1990. Examinations were performed at sea level, at the base camp (5,020 m), and twice at the advanced base camp (5,650 m). Heart rate, left ventricular (LV) end-diastolic volume, cardiac output, mean rate of circumferential fiber shortening, ejection fraction, % fractional shortening, and regional LV wall motion were measured.

At high altitude, heart rate increased to 136% of the sea level value, but gradually decreased in the degree of increment at the early and late advanced base camp measurements. LV end-diastolic volume decreased significantly by 70%. At base camp there were significant increases in ejection fraction, mean rate of circumferential fiber shortening, and % fractional shortening, which showed little change during the long-term stay at high altitude. Regional wall motion at high altitude (measured by the centerline method) decreased at the septal wall and increased at the posterolateral wall. These results demonstrate that: (1) LV cardiac performance at high altitude is enhanced significantly in spite of reduced preload. After good acclimatization, cardiac performance remains augmented, but there is a tendency to decrease the degree of augmentation. (2) In regional LV wall motion, septal wall motion is impaired, but LV posterolateral wall motion shows a compensatory increase.

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The effects of altitude and hypoxia on cardiac function have been extensively researched.[1-9] Although cardiac function was reported to deteriorate under hypoxic conditions, recent reports claim that hypoxia preserves or slightly enhances left ventricular (LV) cardiac contractility.[7-9] However, it is well known that hypoxia induces pulmonary hypertension and right ventricular pressure overload.[10-14] Right ventricular pressure overload hampers LV regional wall motion, especially at the septum.[12,13] However, LV performance at extremely high altitude or in long-term exposure to hypoxia has not been studied. Regional LV wall motion under such conditions is also unknown.

High-altitude cardiac performance has been studied by echocardiography[7,8]; however, previous studies were performed in a hypobaric chamber and at <5000 m in the field. To clarify whether cardiac function can be preserved at higher altitude and during long-term stay is crucial for hypoxia physiology. For that reason, we studied by 2-dimensional echocardiography 11 healthy, climbing members of the Kyoto University Medical Research Expedition to Xixabangma (8,027 m) in 1990 (KUMREX '90) during their entire climbing period of 50 days at the base camp (5,020 m) and the advanced base camp (5,650 m).

METHODS

Subjects: The subjects in this study were the 11 Japanese, climbing members of KUMREX '90. All were healthy men (mean age 34 ± 7 years, range 21 to 43).

All subjects were examined at Kyoto, Japan, for the sea level standard before departure. They had not been at high altitude (>4,000 m) for the previous 6 months and had not acclimated to high altitude. They travelled to Lhasa, China (3,650 m), via Beijing by plane. They travelled from Lhasa to the Xixabangma base camp

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(5,020 m) by car over 8 days. The first echocardiographic examination was performed within 3 days of their arrival at the base camp. The second examination (early period) was performed 20 days later at the advanced base camp (5,650 m) when 7 subjects had been at 7,430 m, 2 at 6,920 m and 2 at 6,340 m. The third set of echocardiograms (late period) was obtained 14 days after the second examination at the advanced base camp (5,650 m) when 9 subjects had reached the summit (8,027 m) and 2 had been at >7,000 m (Figure 1).

Study protocol: Two-dimensional echocardiograms were recorded using a Fukuda Denshi model U-2000 ultrasound system. A 3 MHz mechanical sector probe was used for visualization of 2-dimensional echocardiography. All studies were recorded on 8 mm videotape. Echocardiographic measurements were obtained at rest in the supine 45°, left, semilateral position with electrocardiographic attachments to obtain a simultaneous standard 1-lead tracing. Parasternal and apical long- and short-axis views were obtained. M-mode echocardiography was also performed. LV ejection time was measured as the time between onset of the reduction of the distance separating the LV endocardial surfaces and onset of mitral valve opening, using M-mode echocardiography.

LV dimensions were recorded by passing the ultrasonic beam through the left ventricle immediately distal to the mitral leaflet and measured using the criteria recommended by the American Society of Echocardiography.[15]

Two-dimensional echocardiographic cardiac images were entered into a microcomputer system using an X-Y digitizer and stored in loop format. Analysis of volumes was performed by Simpson's volume equation. Heart rate, end-diastolic volume, cardiac output, mean rate of circumferential fiber shortening, ejection fraction, % fractional shortening and regional left ventricular wall motion were examined.

Mean rate of circumferential fiber shortening (mVcf) was calculated as: $\text{mVcf} = (\text{LVEDD} - \text{LVESD})/(\text{LVEDD} \times \text{LVET})(\text{circ/s})$, where LVEDD was LV minor-axis dimension at end-diastole, LVESD was LV minor-axis dimension at end-systole and LVET was LV ejection time. Percent fractional shortening (%FS) was calculated as: $\%\text{FS} = ([\text{LVEDD} - \text{LVESD}]/\text{LVEDD}) \times 100$.

Regional LV wall motion was measured by the centerline method that has been established as a reliable method to assess LV regional wall motion from contrast LV angiography.[16,17] We applied the centerline method to the 2-dimensional echocardiographic short-axis contour at the high mitral papillary muscle level.

A centerline was constructed by the computer midway between the end-diastolic and end-systolic contour images that were stored in the microcomputer. One hundred equidistant chords were drawn perpendicular to the centerline extending from the end-diastolic to the end-systolic contour. Chord numbering began at the front-end junction of the left and right ventricles, and proceeded clockwise. The length of each chord was the motion of the corresponding point on the LV contour. To adjust for differences in heart size, the shortening fraction (SF) of each chord was calculated as: $\text{SF} = ([\text{chord length}]/[\text{end-diastolic perimeter}]) \times 100$. (Figures 2 and 3.)

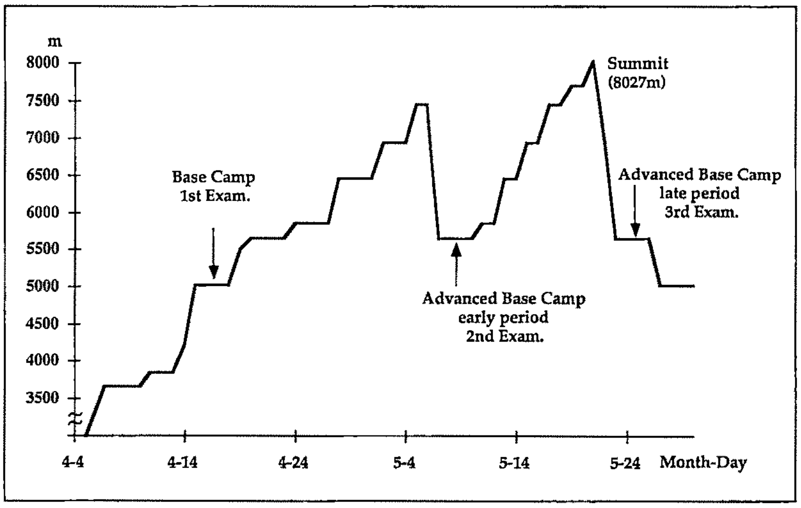
Statistical analysis: All values are expressed as mean ± standard deviation. Statistical analysis was performed using Student's paired t test ($p < 0.05$ was considered significant).

RESULTS

Table I lists the cardiac parameters obtained from the subjects at sea level and during high-altitude exposure.

Heart rate: On ascent to high altitude, heart rate increased significantly compared with that at sea level.

FIGURE 1. Altitude/date profile of expedition showing timing of examination (Exam.).



However, compared with heart rate at base camp there were significant decreases in heart rates at both early and late advanced base camp. There was no significant difference in heart rate between those at early and late advanced base camp (Figure 4).

Left ventricular end-diastolic volume: LV end-diastolic volume significantly decreased at high altitude compared with that at sea level. Although there was no significant difference in LV end-diastolic volume between the base camp and late advanced base camp, LV

TABLE I Heart Rate, Left Ventricular End-Diastolic Volume and Indexes of Left Ventricular Systolic Performance at Sea Level, Base Camp (5,020 m) and Advanced Base Camp (5,650 m) in the Early and Late Periods

	Sea Level	BC	ABC Early	ABC Late
Heart rate (beats/min)	67 ± 11	90 ± 12*	82 ± 10*†	81 ± 15*†
Left ventricular end-diastolic volume (ml)	113 ± 14	79 ± 16*	88 ± 13*†	76 ± 17*‡
Cardiac output (liters/min)	4.9 ± 1.1	5.3 ± 1.0	5.2 ± 0.8	4.4 ± 1.2
Ejection fraction (%)	63 ± 8	76 ± 10*	72 ± 6*	74 ± 5*
Mean rate of circumferential fiber shortening (circ/min)	0.9 ± 0.1	1.6 ± 0.4*	1.5 ± 0.3*	1.3 ± 0.3*
% Fractional shortening	34 ± 5	45 ± 9*	41 ± 5*	42 ± 5*

*p <0.05 vs sea level; †p <0.05 vs BC; ‡p <0.05 vs ABC early.
All values are mean ± standard deviation.
ABC Early = advanced base camp (5,650 m) in early period; ABC Late = advanced base camp (5,650 m) in late period; BC = base camp (5,020 m).

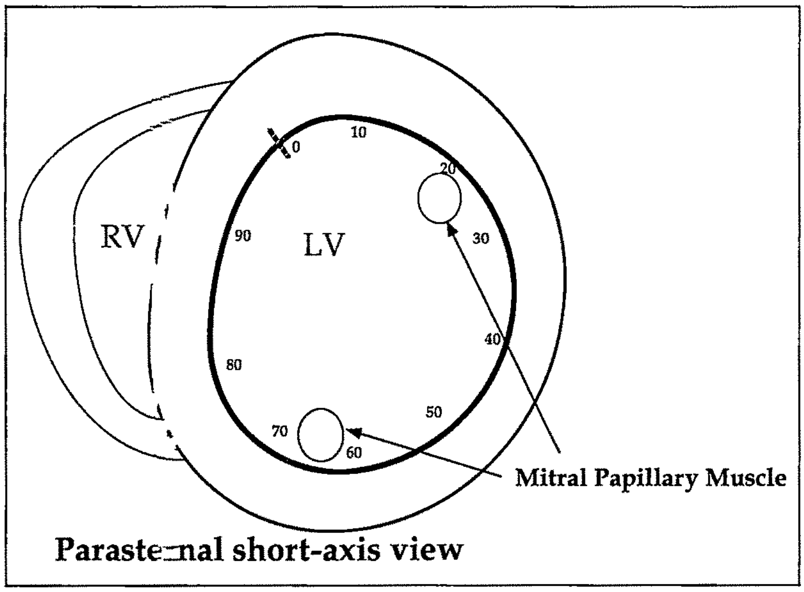


FIGURE 2. Centerline method of regional wall motion analysis. Parasternal short-axis views were obtained at high mitral papillary muscle level. LV = left ventricle; RV = right ventricle.

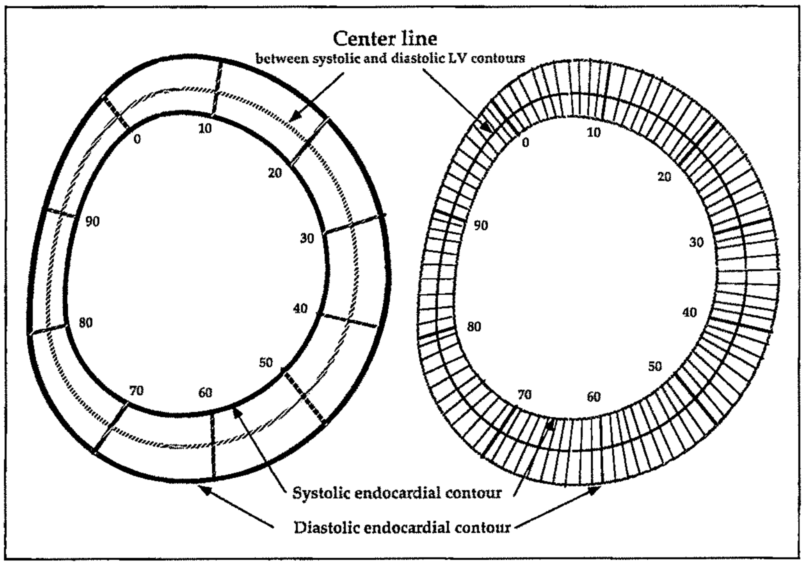

Center line
between systolic and diastolic LV contours
0
10
20
30
40
50
60
70
80
90
Systolic endocardial contour
Diastolic endocardial contour

FIGURE 3. End-diastolic and end-systolic left ventricular (LV) endocardial contours. Centerline was constructed by computer midway between 2 contours. Motion was measured along 100 chords constructed perpendicular to centerline. Chord numbering began at front-end junction of left and right ventricles, and proceeded clockwise.

end-diastolic volume at the early advanced base camp was larger than the other 2 values (Figure 4).

Cardiac output: Cardiac output at high altitude tended to increase in the early stage and decrease in the late stage, although the change was not significant (Figure 4).

Ejection fraction: Left ventricular ejection fraction at high altitude increased significantly compared with that at sea level. There was no significant difference in the values at high altitude (Figure 5).

Mean rate of circumferential fiber shortening: Mean rate of circumferential fiber shortening at high altitude increased significantly compared with that at sea level. Although there was no statistical difference at high altitude there was a tendency to decrease gradually (Figure 5).

Percent fractional shortening: Percent fractional shortening exhibited the same change as that of LV ejection fraction at high altitude (Figure 5).

Regional left ventricular wall motion: Regional wall motion at high altitude (measured by the centerline method) decreased at the septal wall and increased at the posterior wall compared with that at sea-level. In detail, there were significant decreases in segments 84 to 88 of the base camp, 83 to 91 of the early advanced base camp, and 75 to 100 of the late advanced base camp. There were significant increases in segments 32 to 46 of the base camp, 33 to 40 of the early advanced

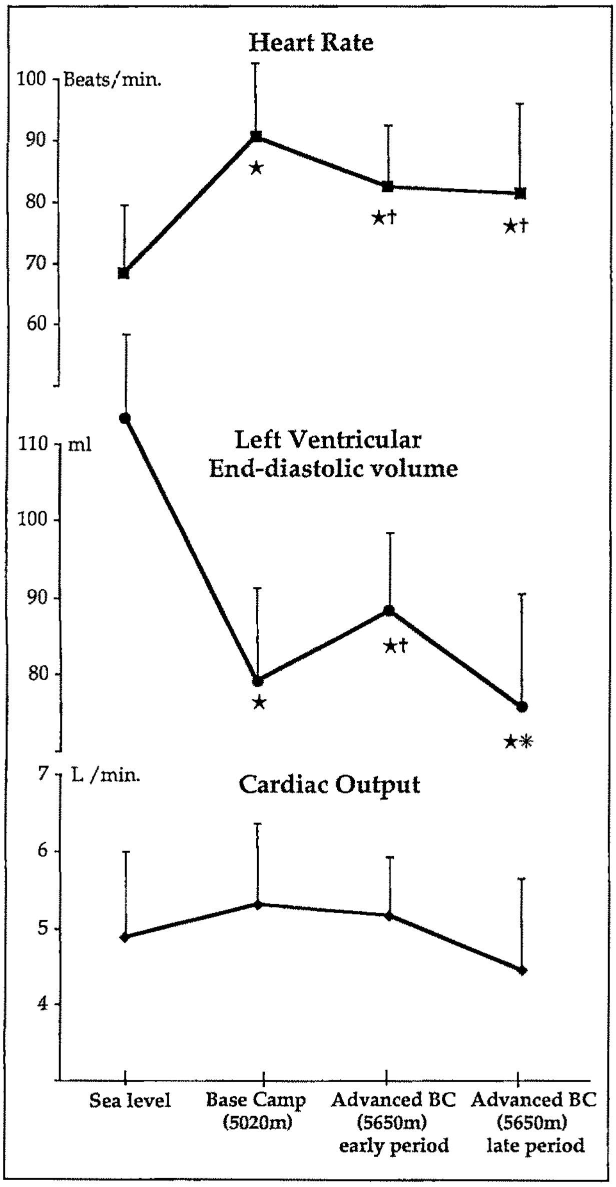


FIGURE 4. Heart rate, left ventricular end-diastolic volume and cardiac output at sea level and high altitude. All values are mean ± standard deviation. ★ $p <0.05$ vs sea level; † $p <0.05$ vs BC; * $p <0.05$ vs advanced ABC early. BC = base camp.

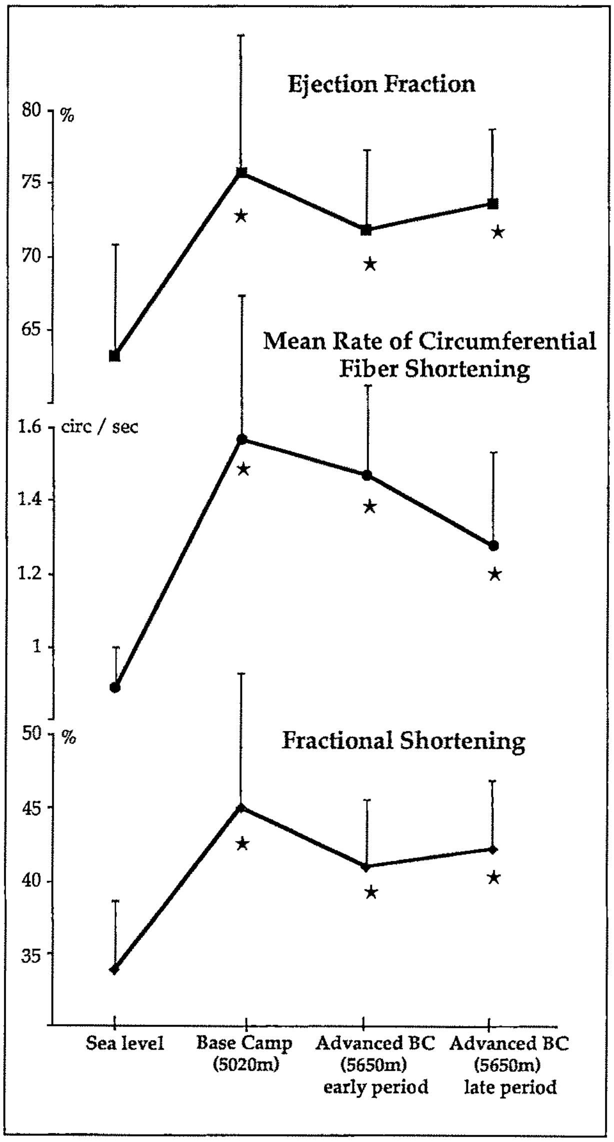


FIGURE 5. Ejection fraction of left ventricle, mean rate of circumferential fiber shortening, and % fractional shortening at sea level and high altitude. All values are mean ± standard deviation. ★ $p <0.05$ vs sea level. BC = base camp.

base camp, and 35 to 39 of the late advanced base camp (Figure 5).

DISCUSSION

There are 2 considerations in understanding cardiac function under hypoxic conditions at high altitude. One is the direct effect of hypoxia on cardiac function. The other is the secondary effect of pulmonary hypertension due to hypoxic pulmonary vasoconstriction.

Although some investigators strongly propounded the development of LV dysfunction at high altitude,[1-6] it has become clear that cardiac function, especially LV function, is maintained or slightly amplified as a direct effect of hypoxia.[7-9] Indeed, using M-mode echocardiography, Fowles and Hultgren[7] reported an augmentation of LV function under hypoxic conditions. Hypoxic cardiac function at simulated high altitude in a hypobaric chamber was reported recently in a well-controlled experiment called Operation Everest II.[8,9,18] Using both cardiac catheterization and 2-dimensional echocardiography, these studies made it clear that cardiac function was not hampered under such experimental conditions.[8,9] However, few studies have examined hypoxic cardiac function at high altitude in the field. Furthermore, there are no long-term studies on hypoxic cardiac function at >5,000 m in the field. We had an opportunity to study cardiac performance and LV regional wall motion at high altitude (5,020 and 5,650 m) for >50 days.

In the early stage of our studies, the heart rate at high altitude increased significantly. LV ejection fraction, mean rate of circumferential fiber shortening and % fractional shortening, which are indexes of LV performance, were significantly greater than those at sea level. Cardiac output on early exposure to high altitude had a tendency to increase, but not significantly. LV end-diastolic volume decreased significantly under high-altitude conditions. Many investigators reported dehydration during high-altitude exposure due to the significant loss of total body water and plasma volume.[19,20] These findings indicate that LV contractility increases at high altitude despite diminished LV end-diastolic volume and preload. Thus, our results are in agreement with reports by other investigators.[7-10] The increases in heart rate and cardiac contractility under hypoxic conditions may be the result of sympathetic stimulation, chiefly through the effect of hypoxia on the carotid bodies.[21-25]

After being at high altitude, long-term cardiac contractility (especially mean rate of circumferential fiber shortening) decreased gradually, although the change was not significant. The other cardiac contractility indexes (ejection fraction and % fractional shortening) in the early and late advanced base camp were slightly lower than those at base camp. Long-term exposure to high altitude also had a negative effect on cardiac output that was parallel to that of mean rate of circumferential fiber shortening. The negative effects of high-altitude exposure on these parameters of cardiac performance may be related to diminished sympathetic tone[24] and down-regulation of sympathetic activity.[26] Heart rate at base camp was the greatest of the 3 high-altitude values, and there was no difference between the values at early and late advanced base camp. In general, heart rate decreased gradually in well-acclimatized subjects at high altitude.[18] At late advanced base camp, the decrease in heart rate stopped, possibly due to hypovolemia, as demonstrated by the decrease in LV end-diastolic volume.

The other significant cardiovascular change at high altitude is the development of pulmonary hypertension due to an increase in pulmonary vascular resistance.[10,14] Pulmonary hypertension induces right ventricular pressure overload and greatly affects ventricular septal wall motion.[12,13] In this study, LV regional wall motion, especially septal wall motion, was examined by 2-dimensional echocardiography. Analysis of regional wall motion was performed with the centerline method that has been verified by LV angiography as an accurate method to assess LV regional wall motion.[16,17]

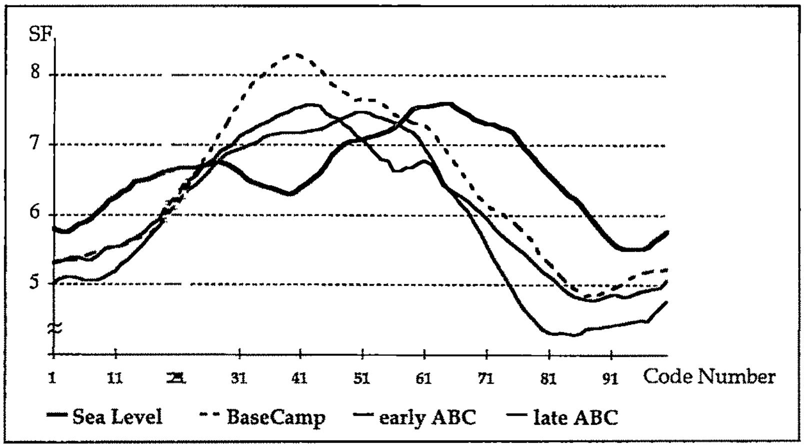


FIGURE 6. Regional left ventricular wall motion with shortening fraction (SF) at sea level and high altitude by centerline method. ABC = advanced base camp.

Furthermore, this method has been validated by 2-dimensional echocardiography in normal subjects and coronary heart patients.[27,28]

Septal wall motion at high altitude was impaired throughout the entire high-altitude period. However, there was a compensatory increase in LV posterolateral wall motion. The impairment of septal wall motion persisted even after long-term stay at high altitude, although the augmentation of posterolateral wall motion had a tendency to decrease as the subjects became acclimatized. The persistence of impaired septal wall motion suggests that the right ventricular pressure overload due to pulmonary hypertension remains unchanged after acclimatization. Sime et al[10] reported that total pulmonary resistance remained elevated in acclimatized lowlanders. Furthermore, some reports revealed that the increased pulmonary vascular resistance in long-term residents at high altitude was secondary to pulmonary arteriolar hypertrophy and that temporary oxygen administration did not relieve pulmonary hypertension.[18,29,30] The continuation of right ventricular pressure overload after acclimatization, as shown by our data, is in agreement with those previous reports.[10,18,29,30] The decreasing tendency to augment posterolateral wall motion could be related to the down-regulation of sympathetic activity[25] and to the decreasing tendency to augment cardiac contractility over time at high altitude.

Acknowledgment: We are indebted to the Goodman Co. for technical support in using the centerline method that was used with 2-dimensional echocardiography. In addition, we would like to thank all members of KUMREX '90 (general leader: Prof. Tobe Takayoshi, MD).

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Coronary Adrenergic Hyperreactivity in Patients with Syndrome X and Abnormal Electrocardiogram at Rest

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Syndrome X is characterized by an abnormal vasomotility of coronary microvessels. It is unknown whether the presence of an ischemic-like pattern in the electrocardiogram at rest (T-wave inversion) reflects a more severe vasomotion disturbance. Changes in coronary sinus flow (thermodilution) and epicardial vessel diameter (quantitative angiography) during adrenergic activation were measured with a standard cold pressor test in patients with syndrome X whose electrocardiogram at rest was normal (group 1: 17 patients) or showed stable, symmetrically inverted T waves (group 2: 22 patients). Cold pressor test increased mean blood pressure and rate-pressure product to a similar extent in both groups, increased coronary sinus flow in group 1 (88 ± 29 to 119 ± 36 ml/min; $p < 0.05$) and not in group 2 (109 ± 37 vs 104 ± 36 ml/min; p = not significant), and decreased coronary resistance in group 1 (1.38 ± 0.42 to 1.19 ± 0.38 mm Hg/ml/min; $p < 0.05$) and augmented it in group 2 (1.06 ± 0.32 to 1.28 ± 0.43 mm Hg/ml/min; $p < 0.02$). During cold stimulus, the proximal and middle segments of epicardial arteries showed negligible changes in their lumen, whereas the distal segment dilated in group 1 (1.81 ± 0.27 to 2.01 ± 0.32 mm; $p < 0.05$) and constricted in group 2 (1.82 ± 0.12 to 1.62 ± 0.20 mm; $p < 0.05$). Differences in coronary hemodynamic and angiographic responses between the groups were statistically significant ($p < 0.05$). The adrenergic test was repeated after administration of intravenous propranolol (0.1 mg/kg) for the following reasons: β blockers are currently used in syndrome X; β blockade may worsen vasoconstriction, leaving α-adrenergic activity unopposed; and consequently, cases like these may worsen with β blockade. After propranolol, cold pressor test maintained the same effects on coronary flow and diameter in group 1, and elicited a weaker vasoconstrictor response in group 2.

Thus, negative T waves in syndrome X identify a subgroup of patients with a vasoconstrictor response to adrenergic activation that involves the microcirculation as well as the distal part of the epicardial branches. In these cases β blockade with propranolol is not detrimental, but appears to be even beneficial.

(Am J Cardiol 1991;68:1698–1703)

Enhancement of vasoconstrictor reactivity as well as attenuation of vasodilator capacity of the coronary circulation have been documented in patients with chest pain and angiographically normal coronary arteries.^{1,2} A sizable proportion of these patients has "non-specific" abnormalities of the repolarization phase of the electrocardiogram at rest.$^{3-8}$ In a few cases, ST-T ischemic-like patterns have been reported.$^{3,6-10}$ However, the clinical significance of this feature has not been elucidated. In the present study we tested whether this electrocardiographic pattern at rest is associated with a peculiar functional coronary disorder. To address this topic we elicited a sympathetic reaction using a standard cold pressor test and analyzed the coronary vasomotor response in patients with syndrome X and negative T waves in the anterior leads compared with that in patients with syndrome X and normal electrocardiogram. Cold pressor test was repeated after administration of propranolol for the following reasons: β blockers are currently used in syndrome X; β blockade may worsen vasoconstriction, leaving α-adrenergic activity unopposed; and consequently, cases like these may worsen with β blockade.

METHODS

Patients: We investigated 39 patients (34 women and 5 men, mean age 54 ± 7 years) with effort-induced chest pain, positive and reproducible exercise

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stress tests (>1 mm ST depression at 80 ms after the J point), and normal coronary arteriograms and left ventriculography, and without left ventricular hypertrophy (echo criteria).

Twenty-four of 39 (62%) patients had episodes of >1.5 mm ST depression during 24 hour Holter monitoring, and 15 (39%) had reversible perfusion defects by thallium-201 stress scintigraphy. No patients presented with typical angina at rest, hypertension (>140/90 mm Hg), diabetes, or valvular and primary myocardial diseases. Previous treatments were withdrawn ≥1 week before patients entered the study; sublingual nitrates were the only drug allowed.

Subjects were divided in 2 groups as having normal electrocardiogram at rest (group 1: 17 cases) or symmetrically inverted T waves at rest >5 mm deep in ≥1 lead with normal baseline ST segment detected in 3 consecutive recordings 1 week apart (group 2: 22 cases). Patients with "non-specific" ST-T changes (low-voltage, flat or diphasic T waves), electrocardiographic abnormalities occurring during activation of the adrenergic nervous system,[11] or secondary to paroxysmal arrhythmias or conduction disturbances[12] were excluded. No significant differences were detected between the groups in regard to age, sex, coronary risk factors, and type and magnitude of noninvasive test response.

Study design: The study was approved by the local ethical committee and written informed consent was obtained from all patients.

Diagnostic coronary angiography was performed with the Judkins technique in multiple projections, using Siemens-Elema equipment with C-arm. Standard hemodynamic measurements were obtained with a Swan-Ganz thermodilution balloon tipped catheter. Blood pressure was recorded with a Pig-Tail catheter (ascending aorta). An 8Fr multithermistor thermodilution pacing catheter (Webster Laboratories) was introduced through the right internal jugular vein and positioned into the coronary sinus. Catheter stability was frequently checked by fluoroscopy and by iced saline solution injections into the right atrium to exclude blood reflux in the coronary sinus.[13]

After diagnostic coronary angiography, baseline systemic and coronary hemodynamics were recorded. Patients initially underwent a standard cold pressor test for 90 seconds.[14] Soon after reversion of the hemodynamic parameters to baseline, propranolol (0.1 mg/kg) was intravenously infused over 15 minutes, and when the expected hemodynamic effects of the drug had occurred (reductions in heart rate and cardiac output), a second cold pressor test was performed. Systemic and coronary hemodynamics, as well as left coronary angiograms (2 views, 90° apart), were consecutively recorded at the peak of the 2 cold pressor tests, and after infusion of propranolol.

Data analysis: Coronary sinus flow was measured according to a previously described method,[15] and coronary resistance was calculated from the ratio of mean aortic pressure and coronary blood flow. Quantitative angiographic measurements were automated by a validated method of digital processing.[16] Briefly, digital images were obtained by viewing each single-frame cineangiographic image with a television camera (RCA 1005 VIDICON) that served as an input to a digital angiographic system (ADAC 4100 C). The computerized analysis of the coronary artery diameter was obtained by means of an interactive computer program with previous magnification of the area of interest and with placement by the observer of a cursor point across the normal vessel diameter. Measurements were obtained in all patients at the proximal, middle and distal thirds of the anterior descending and circumflex arteries, according to the grading criteria for coronary arteries proposed by the American Heart Association.[17] Angiograms were evaluated by 2 independent observers who were unaware of the study phase they were viewing. The masking of the study condition was monitored, and the work of the observers was coordinated by an assistant. Analysis of intra- and interobserver variability for the measurement of the coronary artery diameter showed high reproducibility ($r = 0.97$, standard error of the estimate 3.7% [$p < 0.001$], and $r = 0.98$, standard error of the estimate 3.5% [$p < 0.01$], respectively).

Statistical analysis: Statistical analysis of the data was performed by means of analysis of variance. Data are grouped as mean ± standard deviation.

RESULTS

An example of an electrocardiogram at rest in group 2 is depicted in Figure 1. No changes in the baseline ST-T segment pattern were detected during the study.

Mean hemodynamic and angiographic data for both groups are reported in Tables I and II. Individual responses of coronary flow, resistance and diameter are depicted in Figures 2 through 4.

Hemodynamic and coronary vasomotor responses to cold pressor test before propranolol: Hemodynamic and angiographic data at rest were similar in both groups. During cold pressor test, mean blood pressure and rate-pressure product increased, heart rate and cardiac index were unchanged, coronary sinus flow was augmented in group 1 (88 ± 29 to 118 ± 36 ml/min [+34%]; $p < 0.05$) and steady in group 2 (109 ± 37 to 104 ± 36 ml/min; p = not significant [NS]), and coronary resistance decreased in group 1 (1.38 ± 0.42 to 1.19 ± 0.38 mm Hg/ml/min [−12%]; $p < 0.05$) and

TABLE I Systemic and Coronary Hemodynamic and Angiographic Data at Baseline, During Cold Pressor Test, After Infusion of Propranolol, and During Cold Pressor Test After Propranolol in Group 1

	B	CPT	P	CPT + P
Mean arterial pressure (mm Hg)	106 ± 16	126 ± 18‡	110 ± 15	128 ± 14‡‡
Heart rate (beats/min)	80 ± 10	83 ± 11	66 ± 11§	71 ± 9
Cardiac index (liters/min/m²)	3.7 ± 0.6	3.5 ± 0.7	3.0 ± 0.5§	2.8 ± 0.7
Rate-pressure product (mm Hg × beats/min)	12.8 ± 2.7	15.9 ± 3.4†	10.9 ± 2.1‖	13.8 ± 2.6††
Coronary sinus flow (ml/min)	88 ± 29	118 ± 36*	77 ± 23	101 ± 29
Coronary resistance (mm Hg/ml/min)	1.38 ± 0.36	1.19 ± 0.38†	1.66 ± 0.57	1.41 ± 0.51**
Proximal luminal diameter (mm)	3.26 ± 0.47	3.19 ± 0.40	3.18 ± 0.51	3.22 ± 0.42
Middle luminal diameter (mm)	2.57 ± 0.40	2.54 ± 0.37	2.46 ± 0.41	2.52 ± 0.41
Distal luminal diameter (mm)	1.81 ± 0.27	2.01 ± 0.32*	1.80 ± 0.25	1.96 ± 0.28

*p <0.05; †p <0.02; ‡p <0.01 B vs CPT.
§p <0.05; ‖p <0.01 B vs P.
**p <0.05; ††p <0.02; ‡‡p <0.01 P vs CPT + P.
Data are means ± standard deviation.
B = baseline; CPT = cold pressor test; P = propranolol.

TABLE II Systemic and Coronary Hemodynamic and Angiographic Data at Baseline, During Cold Pressor Test, After Infusion of Propranolol, and During Cold Pressor Test After Propranolol in Group 2

	B	CPT	P	CPT + P
Mean arterial pressure (mm Hg)	105 ± 16	120 ± 11‡	108 ± 12	122 ± 14††
Heart rate (beats/min)	77 ± 11	81 ± 13	64 ± 10§	66 ± 9
Cardiac index (liters/min/m²)	3.2 ± 0.8	3.4 ± 0.7	2.7 ± 0.5	2.8 ± 0.7
Rate-pressure product (mm Hg × beats/min)	12.4 ± 2.9	13.9 ± 3.2†	9.9 ± 2.5‖	11.8 ± 2.3**
Coronary sinus flow (ml/min)	109 ± 37	104 ± 36	91.5 ± 25	98 ± 27
Coronary resistance (mm Hg/ml/min)	1.06 ± 0.32	1.29 ± 0.42†	1.29 ± 0.42	1.32 ± 0.36
Proximal luminal diameter (mm)	3.27 ± 0.35	3.26 ± 0.41	3.11 ± 0.34	3.12 ± 0.31
Middle luminal diameter (mm)	2.48 ± 0.26	2.52 ± 0.34	2.36 ± 0.24	2.35 ± 0.29
Distal luminal diameter (mm)	1.82 ± 0.12	1.61 ± 0.20*	1.70 ± 0.12	1.80 ± 0.12

*p <0.05; †p <0.02; ‡p <0.01 B vs CPT.
§p <0.05; ‖p <0.01 B vs P.
**p <0.02; ††p <0.01 P vs CPT + P.
Data are means ± standard deviation.
Abbreviations as in Table I.

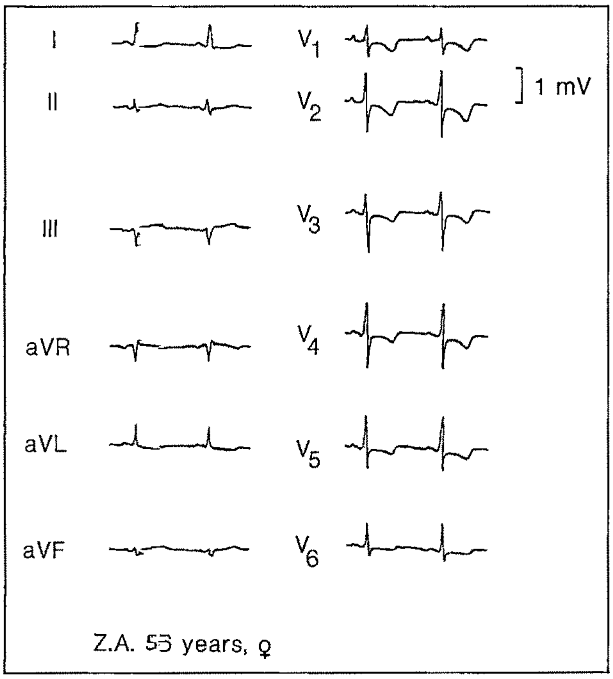

FIGURE 1. Electrocardiographic pattern at rest in group 2 patients.

increased in group 2 (1.06 ± 0.32 to 1.29 ± 0.42 mm Hg/ml/min [+21%]; $p < 0.02$). Group differences in changes of flow and resistance were statistically significant ($p < 0.05$). The lumen of proximal and middle coronary segments had negligible variations; the diameter of the distal segment increased in group 1 (1.81 ± 0.27 to 2.01 ± 0.32 mm [+12%]; $p < 0.05$) and decreased in group 2 (1.82 ± 0.12 to 1.61 ± 0.20 mm [−12%]; $p < 0.05$). Group differences in the changes of the coronary lumen were statistically significant ($p < 0.02$).

Hemodynamic and coronary vasomotor responses to propranolol: Propranolol did not affect mean blood pressure, reduced heart rate, cardiac index and rate-pressure product. Coronary flow decreased and resistance increased to a similar extent in the 2 groups, whereas arterial epicardial lumen was actually unchanged at the proximal, middle and distal sites.

Hemodynamic and coronary vasomotor responses to cold pressor test after propranolol: After β blockade, the response of the systemic circulation to cold pressor test was similar to that before propranolol. Dur-

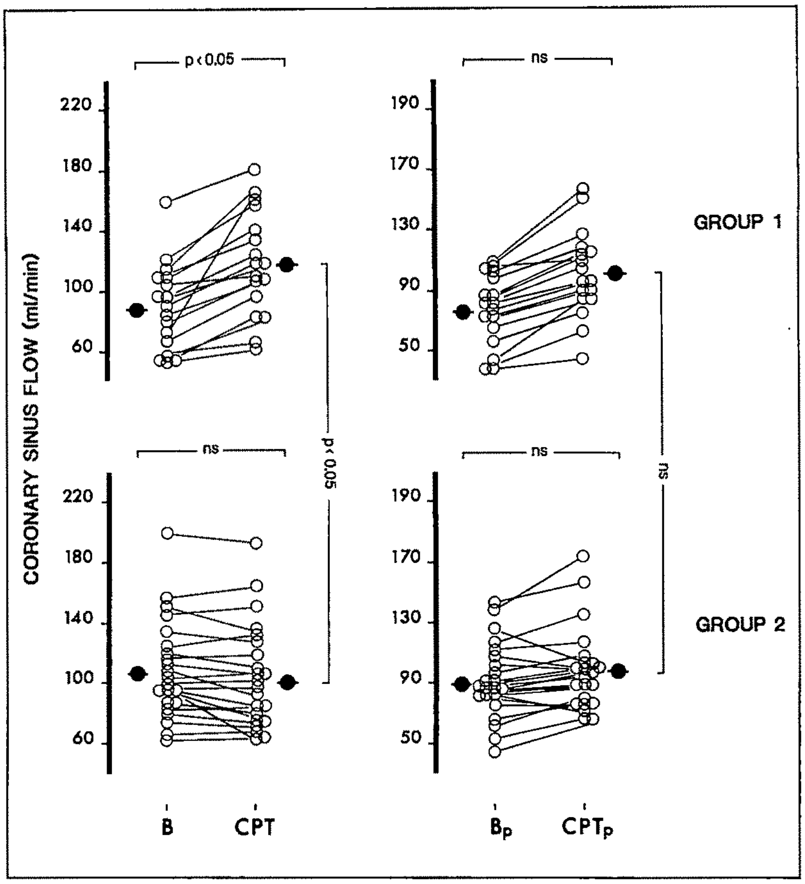

FIGURE 2. Individual changes from baseline (B) of coronary sinus flow in the 2 groups during cold pressor test before (B, CPT) and after (B_p, CPT_p) propranolol. ns = not significant.

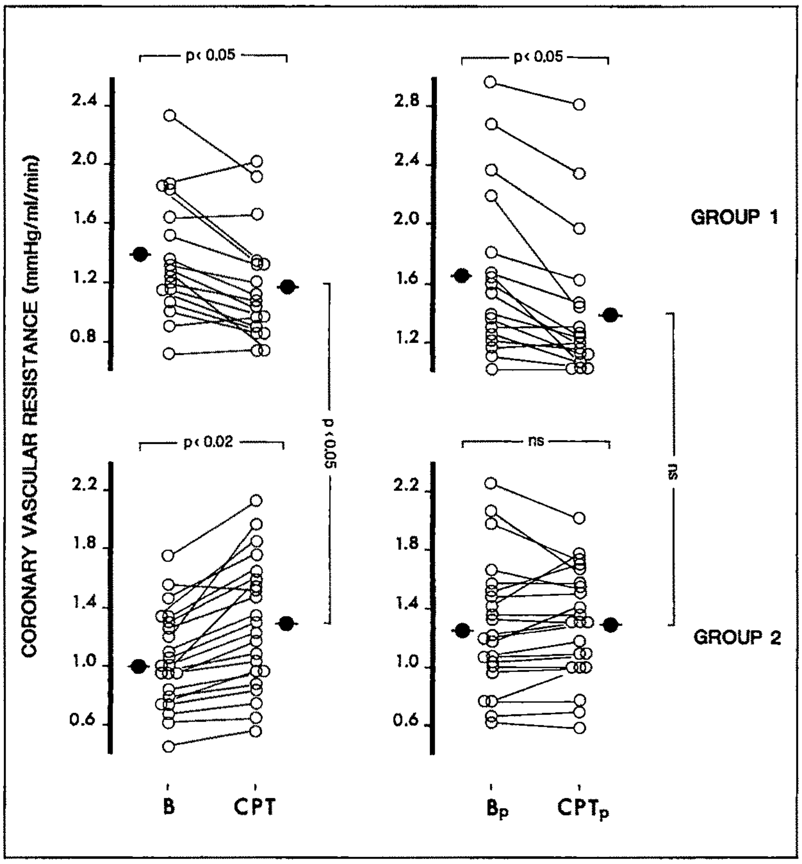

FIGURE 3. Individual changes from baseline (B) of coronary resistance in the 2 groups during cold pressor test before (B, CPT) and after (B_p, CPT_p) propranolol. ns = not significant.

ing the test, coronary sinus flow increased (77 ± 23 to 101 ± 29 ml/min [+24%] [p = NS], and 91.5 ± 25 to 98 ± 27 ml/min [+7%] [p = NS], in groups 1 and 2, respectively), and coronary resistance decreased in group 1 (1.65 ± 0.57 to 1.41 ± 0.51 mm Hg/ml/min [−11%]; $p < 0.05$) and was actually unchanged in group 2 (1.29 ± 0.42 to 1.32 ± 0.36 mm Hg/ml/min; p = NS). Differences between groups in the response of flow and resistance to cold pressor test were no longer detectable after β blockade. Under the stimulus of cold, the distal coronary diameter increased in group 1 (1.80 ± 0.25 to 1.96 ± 0.28 mm [+9%]; p = NS) and 2 (1.70 ± 0.12 to 1.80 ± 0.12 mm [+6%]; p = NS). There were no significant differences between groups in the response of the epicardial coronary branches to cold pressor test.

DISCUSSION

A modest increase in coronary blood flow and in diameter of the large epicardial vessels during cold pressor test has been documented in previous studies.[1,18-20] Flow changes probably reflect the net result of a predominant metabolic-mediated dilatation secondary to the increase in myocardial oxygen demand, and of the effect of coronary vasoconstriction due to concomitant α-receptor activation. The associated relaxation of large coronary arteries likely results from the release of endothelial-dependent vasodilator substances.[21]

In the present study, the cold pressor test elicited coronary vasomotor responses that were opposite in the 2 groups. Changes in flow and resistance indicate that the response was appropriate (vasodilatation) in group 1 and inappropriate (vasoconstriction) in group 2. The vasomotor behavior of the distal part of the epicardial coronary arteries was similar to that of the microcirculation. This suggests that the same adrenergic hyperreactivity of arterioles involves the distal portion of the epicardial circulation. The reasons for the peculiar response of patients in group 2 are not easily understood. Changes in coronary perfusion pressure and myocardial oxygen demands were similar in both groups. The influence of excessive extravascular resistance due to myocardial hypertrophy or tachycardia seems unlikely, because of the normal left ventricular anatomy and absence of significant changes in heart rate during the test. Enhanced neurohumoral discharge may be a potential cause of the constrictor response in group 2. The lack of catecholamine plasma determinations during cold pressor test is an obvious limitation to this interpretation. However, evidence exists that α-receptor activation by cold pressor test can induce coronary vasoconstriction in some patients with ischemic heart disease.[22-24] This effect may involve the coronary tree at different levels depending on regional differences in α-receptor concentration, distribution and sensitivity.[25-28] Recent clinical studies have also considered that an enhanced sympathetic drive may be involved in the

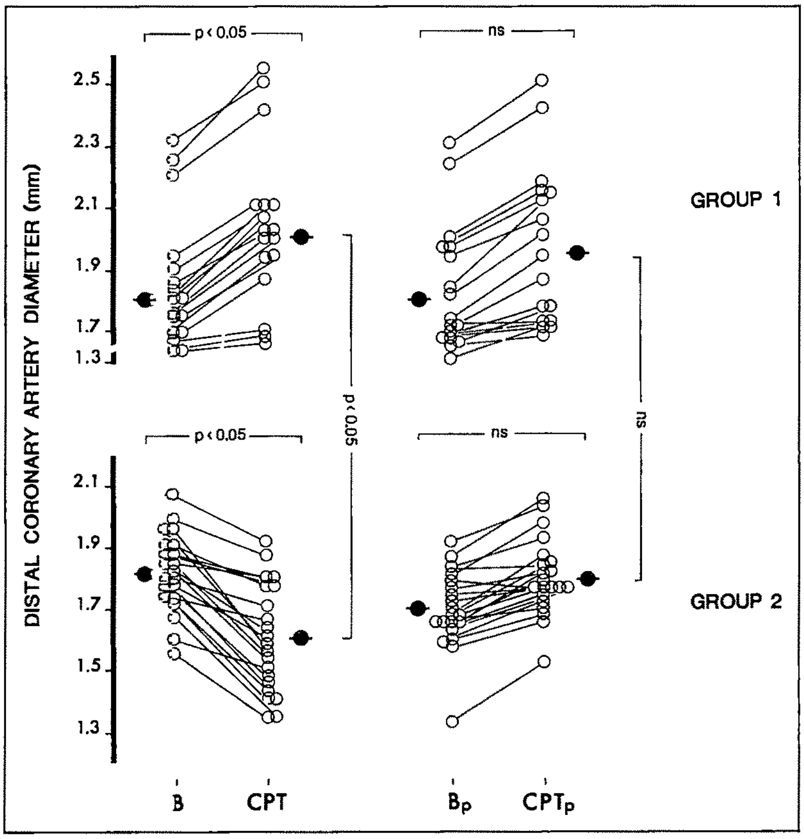

FIGURE 4. Individual changes from baseline (B) of luminal diameter of distal coronary segment in the 2 groups during cold pressor test before (B, CPT) and after (B_p, CPT_p) propranolol. ns = not significant.

genesis of myocardial ischemia in syndrome X.[23,29–32] Therefore, the hypothesis that an increased sensitivity of coronary micro- and macrocirculation to adrenergic influences is a potential cause of vasoconstriction in patients in group 2 seems reasonable. The link between coronary vasomotor behavior and electrocardiographic appearance in these patients remains unclear.

Beta blockers have proven to be effective in syndrome X and are currently used for its treatment.[33,34] Because β blockade may leave the coronary vasoconstrictor influence of α-adrenergic receptors unopposed, we considered testing the possibility of a deleterious effect of propranolol. Despite these theoretical considerations, the drug appeared to be able to temper the vasoconstrictor reaction in group 2. An interpretation of these results may be that of a facilitation by propranolol of parasympathetic activity promoted by cold pressor test[35] and of vagal-related coronary dilatation.[36–38] These effects may oppose the α-adrenergic constrictor effect of cold stimulation. Whether propranolol in the long-term benefits patients with syndrome X and negative T waves remains to be proved.

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Gender Differences in Left Ventricular Anatomy, Blood Viscosity and Volume Regulatory Hormones in Normal Adults

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Gender differences in left ventricular (LV) anatomy, whole blood and plasma viscosity, and blood volume regulatory hormones were studied in 110 normotensive employed adults (28 black and 34 white men [mean age 51 ± 12 years], 20 black and 28 white women [mean age 53 ± 12 years]). LV mass and wall thicknesses were positively related to whole blood viscosity, primarily because of higher values of both variables in men. LV chamber size was inversely related to hematocrit and to blood viscosity ($p < 0.002$) in women but not in men. Whole blood viscosity increased with age in men ($p < 0.01$), but tended to decrease in women; older women also had better LV function, larger LV chambers, and a trend toward increasing LV mass. Atrial natriuretic factor increased with age in women but not in men ($r = 0.60$, $p < 0.001$), and plasma renin activity decreased ($r = -0.35$, $p < 0.02$). Thus, in women, increase in LV chamber size with age and associated changes in LV systolic function, atrial natriuretic factor levels and plasma renin activity suggest plasma volume expansion related to the aging process. These findings also suggest that an increase in LV volume load with age may contribute to previously reported increases in LV mass in older women.

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Left ventricular (LV) anatomy and function differ between normotensive men and women.[1-5] Experimental manipulation of sex hormones affects cardiac size,[6,7] suggesting direct endocrine regulation of the myocardium. However, gender differences in hemodynamic load may also affect cardiac geometry and function.[5-8] In addition, whole blood viscosity—the rheologic component of peripheral resistance and a stimulus to LV hypertrophy[9,10] — is lower in normal women than in men,[11,12] and plasma renin activity and its relation to other variables also differ between women and men,[13] suggesting gender differences in sodium-volume homeostasis.

These and other observations[14,15] suggest that gender-specific factors affect cardiac load, size and performance. Accordingly, the present study examines whether gender differences in LV anatomy and function are related to blood viscosity or blood volume regulatory hormones, and whether alterations in these parameters with age parallel the reported increase in LV mass with age in women.[16]

METHODS

Subjects: One hundred twenty-one subjects were studied, representative of normotensive members of a large employed population in New York City that has been previously reported on in part.[2,3,12] Eligible subjects had no historical, clinical or laboratory evidence of cardiovascular, respiratory, endocrine, hepatic, renal or hematologic disorders, abnormal hemoglobin or hematocrit value, and were free of medications. Eleven subjects (9%) were excluded because M-mode echocardiograms did not meet standard criteria for technical quality[17]: the 110 remaining subjects consisted of 28 black men (52 ± 9 years old), 20 black women (50 ± 10 years old), 34 white men (51 ± 13 years old) and 28 white women (54 ± 12 years old).

Procedures: After informed consent had been obtained, blood was collected to determine whole blood viscosity, creatinine, plasma renin activity and atrial natriuretic factor on the same morning as echocardiographic study and completion of 24-hour urine collec-

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TABLE I Influence of Gender and Race on Blood Viscosity, Hormonal Profile and Left Ventricular Anatomy

	Men (n = 62)	Women (n = 48)	p Value	Effect of Black Race
Whole blood viscosity				
208 s^{-1} (cp)	4.73 ± 0.58	4.11 ± 0.46	<0.00001	----
104 s^{-1} (cp)	4.97 ± 0.62	4.33 ± 0.48	<0.00001	----
52 s^{-1} (cp)	5.57 ± 0.70	4.92 ± 0.61	<0.00001	----
Hematocrit (%)	46 ± 3	41 ± 3	<0.00001	----
Plasma viscosity (cp)	1.38 ± 0.11	1.40 ± 0.10	<0.32	----
Plasma renin activity (ng/ml/hour)	2.37 ± 1.69	2.10 ± 1.68	<0.34	----
Atrial natriuretic factor (fmol/ml)	10.88 ± 5.18	14.66 ± 8.63	<0.03	----
LV diastolic dimension index (cm/m^2)	2.63 ± 0.27	2.73 ± 0.27	<0.06	Decrease (p <0.03)
Posterior wall thickness (cm)	0.86 ± 0.12	0.79 ± 0.08	<0.0004	Increase (p <0.03)
Interventricular septal thickness (cm)	0.94 ± 0.13	0.85 ± 0.11	<0.0002	----
LV mass index (g/m^2)	83.35 ± 20.32	68.91 ± 15.87	<0.0001	----
LV mass/lean body mass (g/kg)	3.19 ± 1.15	2.88 ± 0.80	<0.13	----

cp = centipoise; LV = left ventricular.

tion to measure creatinine excretion. Arterial blood pressure was measured by arm cuff and mercury manometer with the subject recumbent at the end of echocardiography, using the first and fifth Korotkoff phases as systolic and diastolic pressure, respectively.

Laboratory measurements: Blood samples were obtained, without stasis, from the antecubital vein between 9 A.M. and noon, after an overnight fast. Microhematocrit, whole blood viscosity at shear rates of 208, 104, 52, 5.2, 0.5 and 0.1 s^{-1} and plasma viscosity (reported as the average of values at 52 and 0.5 s^{-1}) were measured as previously reported.[12,18,19] Plasma renin activity and atrial natriuretic factor were determined by radioimmunoassay, as previously described.[20,21] Urinary creatinine was also measured by standard analytical techniques.

Echocardiographic measurements: Two-dimensionally targeted M-mode echocardiograms were recorded as previously described[22] with the subjects in a partial left decubitus position, and recorded on strip-chart paper at 50 mm/s. All subjects exhibited normal wall motion on 2-dimensional echocardiogram. M-mode recordings, performed with the ultrasound beam at or just below the mitral valve tips, were coded and interpreted by 2 investigators unaware of subjects' clinical status and test results. Measurements of interventricular septal thickness, posterior wall thickness and LV diastolic dimension were obtained using a sound-pen digitizer interfaced to a computer, according to the American Society of Echocardiography and the Penn conventions.[23,24] Standard methods were used to calculate LV mass, fractional shortening and end-systolic stress.[24-27] End-systolic stress-adjusted LV fractional shortening was used as an index of LV performance independent of afterload.[22]

LV mass and end-diastolic dimension were normalized for body surface area (m^2). LV mass was also divided by lean body mass, estimated from 24-hour urinary creatinine excretion, by a previously reported regression equation.[2,28]

Statistical analysis: Data are expressed as mean ± 1 standard deviation. One- or 2-way analysis of variance was used to assess the effect of gender or of gender and race (by hierarchical procedure). Gender differences were controlled for race by using analysis of covariance. Least-squares linear correlation, partial correlation and multiple linear regression were used to study relations among variables. The null hypothesis was rejected at $p < 0.05$.

RESULTS

General characteristics of the population: Men and women had comparable blood pressure (129 ± 11/78 ± 8 and 130 ± 13/79 ± 9 mm Hg, respectively) and body mass index (26 ± 3 and 26 ± 5 kg/m^2, respectively). Black race was associated with higher values of blood pressure ($0.005 < p < 0.0001$).

Blood viscosity and hormonal profile (Table I): Whole blood viscosity was higher in men than in women at all shear rates owing to a difference in hematocrit, with comparable plasma viscosity. Plasma renin activity

TABLE II Demographic Characteristics of Age-Grouped Normal Adults

	Age 18–54		Age 55–74	
	Women (25)	Men (34)	Women (23)	Men (28)
Age (years)	43 ± 7	43 ± 7	63 ± 4	62 ± 5
Race (black/white)	13/12	17/17	7/16	11/17
BMI (kg/m^2)	28 ± 6	26 ± 4	25 ± 4	25 ± 2
SBP (mm Hg)	127 ± 12	126 ± 10	134 ± 14	132 ± 11
DBP (mm Hg)	79 ± 10	78 ± 8	78 ± 7	80 ± 8

BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure.

TABLE III Age-Related Gender Difference in Whole Blood Viscosity, Hematocrit and Plasma Viscosity

	Age 18–54				Age 55–75		
	Women (25)		Men (34)		Women (23)		Men (28)
Blood viscosity							
208 s^{-1} (cp)	4.19 ± 0.56	*	4.58 ± 0.45	‡	4.03 ± 0.32	†	4.91 ± 0.68
104 s^{-1} (cp)	4.44 ± 0.58	*	4.80 ± 0.47	‡	4.22 ± 0.3	†	5.18 ± 0.72
52 s^{-1} (cp)	4.99 ± 0.62	*	5.36 ± 0.56	‡	4.85 ± 0.61	†	5.81 ± 0.79
Hematocrit (%)	41.8 ± 3.40	*	44.8 ± 3.02	‡	41.0 ± 2.0	†	46.4 ± 3.51
Plasma viscosity (cp)	1.40 ± 0.12		1.36 ± 0.11		1.38 ± 0.08		1.41 ± 0.12

*p <0.01; †p <0.0001.
‡p <0.04; gender difference in age-related trend (2-way analysis of variance).
Analysis controlled for the effect of race (analysis of covariance).
cp = centipoise.

TABLE IV Age-Related Gender Differences in Left Ventricular Anatomy and Function

	Age 18–54				Age 55–74		
	Men (34)		Women (25)		Men (28)		Women (23)
LV mass index (g/m²)	81.1 ± 16.8	‡	65.1 ± 12.8		86.0 ± 24.0	*	73.0 ± 18.0§
LV diameter index (cm/m²)	2.62 ± 0.27		2.66 ± 0.22		2.64 ± 0.29	*	2.81 ± 0.30
Fractional shortening (%)	34.9 ± 6.1		35.8 ± 2.7		36.1 ± 5.13	*	39.5 ± 6.18‖
ESS-adjusted FS (%)	36.0 ± 3.0		35.8 ± 3.1	¶	35.8 ± 3.8	†	38.5 ± 3.9

Statistical significance: *p <0.05; †p <0.01; ‡p <0.0005.
Age effect: §p <0.05; ‖p <0.01.
¶p <0.03 significant gender-differences in the effect of age.
ESS = end-systolic stress; FS = fractional shortening; LV = left ventricular.

was similar in men and women, whereas atrial natriuretic factor was higher in women than in men.

Gender and race differences in left ventricular geometry (Table I): Mean LV mass was 37% higher in men than in women, but LV mass/lean body mass did not differ significantly between genders. Black race was associated with smaller LV chamber size and thicker LV posterior wall. As a result, relative wall thickness was greater in black than in white subjects (0.35 ± 0.05 vs 0.33 ± 0.04, $p < 0.04$).

Correlates of left ventricular anatomy: In the entire sample, at each shear rate from 0.1 to 208 s^{-1}, whole blood viscosity was directly related to septal thickness ($r = 0.20$ to 0.22, all $p < 0.03$), posterior wall thickness ($r = 0.32$ to 0.33, all $p < 0.001$) and LV mass index ($r = 0.19$ to 0.24, $0.01 < p < 0.05$). However, these relations were mostly dependent on gender, and were not significant when considered in women and men separately. Direct relations were also found between LV mass index and both systolic ($r = 0.23$, $p < 0.02$) and diastolic ($r = 0.19$, $p < 0.05$) blood pressure.

Although LV wall thicknesses were positively related to whole blood viscosity, LV end-diastolic dimension index, the third anatomic determinant of LV mass index, was inversely related to whole blood viscosity at all shear rates ($r = -0.20$ to -0.25, $0.007 < p < 0.04$), mainly because of the strong relation found in women ($r = -0.43$ to -0.53, all $p < 0.002$).

Effects of aging on gender-related differences: Stratification for age was based on the probability of menopause in women. Fifty-five years of age was chosen as a partition value, because very few women older than this age have regular periods.[29] Demographic characteristics of women and men in the 2 age strata were similar (Table II).

Blood viscosity: Age had no effect on whole blood viscosity in the entire sample, because of opposite age relations in men and women. Whole blood viscosity at all shear rates increased with age in men ($r = 0.33$ to 0.39, $0.002 < p < 0.01$), whereas it tended to decrease in women (partial $r = 0.34$ to 0.40 in men and -0.13 to -0.18 independently of the effect of race). Consequently, the gender difference in blood viscosity and hematocrit was more marked in older than in younger subjects (Table III). No relation existed between age and plasma viscosity.

Left ventricular anatomy and function (Table IV): The gender difference in LV mass index was less apparent in older than in younger subjects, whereas LV diameter index became statistically larger in older women than in men. Furthermore, LV fractional shortening and afterload-corrected fractional shortening were higher in women >55 years than in men of the same age.

Blood volume regulatory hormones: No relation was found between age and plasma renin activity in the entire group, whereas a weak direct relation existed with atrial natriuretic factor (n = 66, r = 0.33, standard error of the estimate = 7 fmol/ml, p <0.008). Figure 1 shows that atrial natriuretic factor was related to age in women (r = 0.60 [n = 27]) but not in men; controlling for the effect of race did not change this relation (partial r = 0.56 in women). Thus, older women had higher atrial natriuretic factor levels than older men (21 ± 9 vs 10 ± 5 fmol/ml, p <0.0003), whereas no difference was found in younger subjects (11 ± 5 and 12 ± 6 fmol/ml in women and men, respectively). Similarly, plasma renin activity was inversely related to age in women (r = −0.35, standard error of the estimate = 1.6 ng/ml/hour, p <0.02 [n = 45]), but not in men; the relation in women was even stronger when the effect of race was removed (partial r = −0.41).

DISCUSSION

Relation of age and gender to left ventricular size and function: In the present study, LV chamber dimension indexed for body surface area was greater in older women than in men, but not in younger subjects; in contrast, LV mass index was greater in men than in women in both age strata, a difference that was slightly attenuated in the older subjects. These results parallel the positive relation between age and LV mass found in women and the absence of such a relation among men in apparently healthy participants in the Framingham Heart Study.[16] Cabral et al[7] demonstrated that in hypertensive male rats the presence of testosterone facilitated the development of LV hypertrophy, whereas pretreatment with estradiol inhibited LV growth; moreover, orchiectomy of male and oophorectomy of female rats attenuated and enhanced the development of LV hypertrophy, respectively. Thus, in fertile women, sex hormones may inhibit LV growth. Because LV mass is the strongest risk factor other than age for cardiovascular morbid events,[30,31] increasing LV mass may contribute to the partial loss of cardiovascular protection among older women.

The age-related gender differences in LV chamber size that were observed suggest that loading conditions may change in postmenopausal women. The increase in diastolic LV chamber size in older women was not due to reduced LV performance: to the contrary, systolic function was enhanced. These findings could be consistent with a Starling mechanism, if expansion of plasma volume led to an increase in cardiac preload. The age-related increase in atrial natriuretic factor (Figure 1), decrease in plasma renin activity, and tendency toward a decrease in blood viscosity in older women, are all in the direction that would be produced by an expansion of plasma volume. Unfortunately, direct measurements of plasma volume were not obtained in this study, because Evans blue dye was not available during this study and few subjects would accept use of radioisotopes.

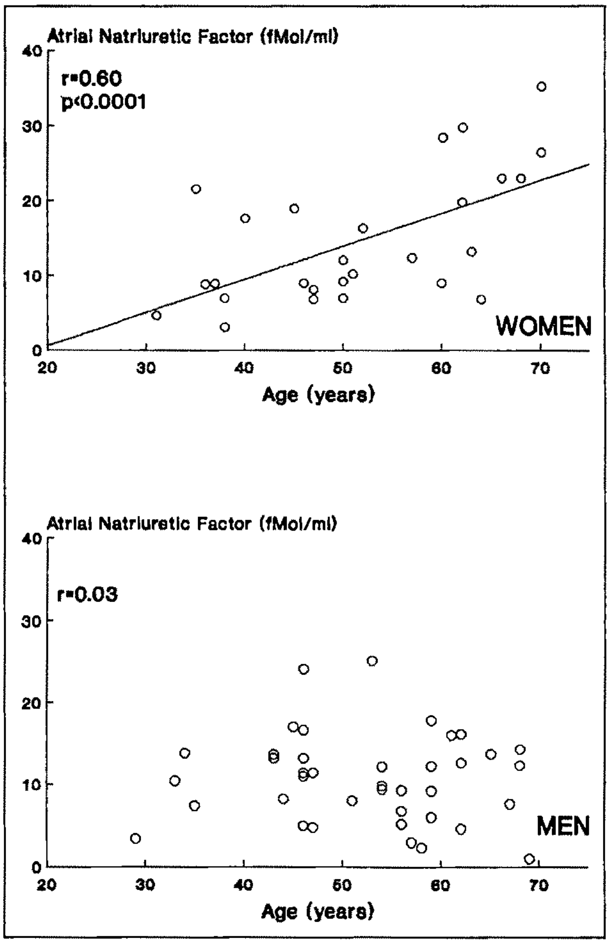

FIGURE 1. Relation of atrial natriuretic factor *(vertical axis)* to age *(horizontal axis)* in normotensive adults. The relation is significant in women but not in men.

Whole blood viscosity and left ventricular mass: Whole blood viscosity was weakly related to LV mass in our normal subjects, because deviations of whole blood viscosity within the normal range had opposite relations to the anatomic components of LV mass (direct to LV posterior wall thickness, and inverse to chamber dimension). Therefore, changes in blood viscosity may influence LV geometry more than LV mass.

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Cost-Effectiveness Analysis of the Use of Digoxin Immune Fab(Ovine) for Treatment of Digoxin Toxicity

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Each year many people have digitalis toxicity severe enough to require extensive hospital treatment. Digoxin immune Fab[ovine]-Fab fragments (Digibind®) have been shown to reverse digitalis toxicity and substantially reduce the risk of death. Data were used from uncontrolled studies of patients treated with Fab fragments as well as clinical, medical care and pharmacokinetic data from symptomatically treated patients to derive estimates of the difference in clinical outcomes and medical care costs when treating with this new drug. Estimates are derived separately for treatment of patients with toxicity that is immediately life-threatening and patients whose manifestations are not immediately life-threatening. Treatment with Fab fragments reduces the probability of dying more for the seriously toxic than for the less seriously toxic patient. Such treatment is generally associated with an increase in total medical care costs for the seriously toxic patients because more of them survive the toxic episode and require additional medical care before discharge from the hospital. For these patients, the estimated cost per life-year saved is between $1,900 and $5,400. When Fab fragments are used to treat less seriously toxic patients, total medical care costs decrease because of an estimated decreased number of days in the coronary care unit and decreased use of pacemakers and other aggressive treatments.

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Digitalis toxicity is believed to occur in 5 to 20% of all patients being treated with digitalis glycosides.[1] Because the therapeutic and toxic ranges in patients with heart disease are relatively close, toxicity during chronic use may result from an accidental overdose, unpredictable changes in kidney function, or electrolyte imbalance. Most of the cases of toxicity are minor and the patient can be treated by temporary withdrawal or reduction in the dose of digoxin either on an outpatient or inpatient basis. However, several thousand patients each year require more aggressive hospital treatment. Most of the cases of digitalis toxicity occurring during the course of chronic therapy ("therapeutic toxicity") are caused by digoxin, because it accounts for >90% of digitalis use in the U.S. Acute toxicity is less common, approximately 2,400 cases each year[2] and is seen mostly in 2 groups: young children accidentally eating tablets and adults attempting suicide by overdose.

Until recently the standard treatment for patients with significant clinical symptoms of toxicity was symptomatic and included the following, as necessary: electrolyte maintenance, antiarrhythmic agents, a temporary pacemaker, direct-current countershock, and cardiac massage. The half-life of digoxin is estimated to range from 36 to 48 hours for patients with normal kidney function, to 4 to 6 days for patients with severely compromised kidney function.[3] Thus, digoxin levels may take several days to fall below the toxic range. For this reason, these patients often required lengthy stays in the coronary care unit. Even with extensive and aggressive symptomatic treatment, reported mortality rates have ranged from 3 to 21% for patients who became toxic during maintenance therapy with digoxin[4] and from 13 to 25% for those with suicidal or accidental ingestion.[5]

Data from clinical trials indicate that using digoxin immune Fab[ovine]–Fab fragments (Digibind®) for the treatment of digoxin toxic patients who are experiencing serious clinical manifestations substantially reduces their risk of death.[6] Fab fragments are presently indicated for use in patients with potentially life-threatening cardiac arrhythmias or other evidence of severe digitalis intoxication. Such patients require continuous monitoring until the digoxin levels are reduced into the

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therapeutic range. Treatment with Fab fragments is expected to reduce the mortality and morbidity in these patients. Before Fab fragments were approved for use, an appropriate safety profile was established. Physicians, pharmacists, and third party payers are also likely to want to know under what conditions the benefits associated with the expected reductions in mortality and morbidity outweigh the increased drug costs.

In this article, we estimate the benefits and costs of using Fab fragments for patients with more and less serious manifestations of toxicity. The data we used for these estimates are from uncontrolled trials and were not collected for the purpose of cost-effectiveness analysis. In addition, the values for several key data items had to be derived from the available data using expert judgement. For these reasons, we also describe the sensitivity of our results to alternative possible values for these data items.

METHODS

When Fab fragments are used to treat a patient with digoxin toxicity both the clinical outcomes and medical care services used during the toxic episode change. In this study, we estimate changes in the following clinical outcome and medical care service use associated with using Fab fragments: survival rate from toxic episode; length of stay in the coronary care unit (intensive care); length of stay in the hospital; and probability of temporary pacing, electrical cardioversion, or cardiac massage, or a combination.

We use the estimates of the changes in clinical outcome and medical care service use to estimate the benefits and costs of using Fab fragments. In addition, we estimate the net costs, difference between all costs and all benefits that can be assigned a dollar value, and the net cost/effectiveness ratio where effectiveness is measured as the expected gains in life-years using Fab fragments.

Patient groups analyzed: Expected clinical outcomes and medical care use vary according to the degree of digoxin toxicity and the patient's baseline state of health. Four groups of patients were identified for analysis in our study: (1) adults with heart disease who accidentally become toxic during digoxin therapy, (2) adults with heart disease who ingest digoxin with suicidal intent, (3) adults with no heart disease who ingest digoxin with suicidal intent, and (4) children <5 years old with no heart disease who accidentally ingest digoxin. A potential fifth group, composed of children with cardiac diseases are not considered in the analyses.

Each of these 4 groups of patients can be further divided into 2 subgroups: (I) patients who have cardiac manifestations that are immediately life-threatening (e.g., ventricular tachycardia, ventricular fibrillation, or third-degree heart block); and (II) patients who have less serious cardiac manifestations such as ventricular premature contractions (stable or increasing in complexity), first- or second-degree heart block (stable or increasing), or massive ingestion of digoxin without immediately life-threatening arrhythmias.

Assumed outcomes of toxicity episode: We assume that an episode of digoxin toxicity results in 1 of 3 possible outcome scenarios: (1) patient survives the toxic episode after drug treatment only; (2) patient survives the toxic episode after receiving drug therapy and aggressive nondrug therapy such as a temporary pacemaker, cardioversion and cardiac massage; and (3) patient dies during the toxic episode despite receiving drug treatment and, possibly, aggressive nondrug therapy. Figure 1 illustrates these 3 outcome scenarios.

We make the simplifying assumption that surviving patients return to their baseline state of health once the toxic episode is over. This baseline state of health varies according to whether the patient has heart disease and whether the ingestion was suicidal or accidental.

Changes in outcomes with Fab fragments: We compute the reduction in the probability of dying and change in medical care service use associated with using Fab fragments for each patient subgroup using the probabilities shown in Figure 1 as follows:

$$\text{Change in probability of dying} = P_3^D - P_3^{ND}$$

$$\text{Change in service use } S_j = \sum_{i=1}^{3} (P_i^D \times S_{ij}^D) - (P_i^{ND} \times S_{ij}^{ND})$$

where the i's are the 3 outcome scenarios and the S_{ij}'s are the different types of medical care service j including hospital days, intensive care days, cardioversion, pacemaker, and cardiac massage in outcome scenario i.

Dollar values are assigned to changes in medical care use based on estimated costs of the individual services. The net costs of using Fab fragments are computed as the sum of the cost of the Fab fragments and the estimated dollar costs of all the increases in medical care use, minus the estimated dollar costs of all decreases in medical care use.

RESULTS

Parameter estimates: The parameter estimates and their sources are presented in Tables I through III. In some cases the parameter values are obtained directly from experimental data. Data for patients treated with Fab fragments are available from Burroughs Wellcome's multicenter trial[6] and postmarketing surveillance study.[7] The data from the postmarketing surveillance study are more representative of actual clinical practice and are used for all patient groups except children with life-threatening manifestations. Because the

TABLE I Percentage of Patients with Each Clinical Outcome Scenario by Severity of Manifestations and Type of Treatment

	Patient Groups*			
	A	B	C	D
Immediate Life-Threatening Clinical Manifestations				
Without Fab fragments				
Surviving with drug treatment only	0	0	0	0
Surviving with aggressive treatment	33	33	50	50
Dying	67	67	50	50
With Fab fragments				
Surviving with drug treatment only	54	55	60	75
Surviving with aggressive treatment	18	15	40	15
Dying	28	30	0	10
Potentially Life-Threatening Clinical Manifestations				
Without Fab fragments				
Surviving with drug treatment only	35	35	50	50
Surviving with aggressive treatment	35	35	30	30
Dying	30	30	20	20
With Fab fragments				
Surviving with drug treatment only	86	76	89	100
Surviving with aggressive treatment	0	13	11	0
Dying	14	11	0	0

*Group A = therapeutic/heart disease; group B = suicide/heart disease; group C = suicide/no heart disease; group D = accident/child/no heart disease.
Sources: references 6 (patients 38 to 150) to 10.

TABLE II Percentage of Patients Needing Aggressive Treatment Who Received Pacing, Cardioversion and Cardiac Massage

	Patient Groups*			
	A	B	C	D
Immediate Life-Threatening Manifestations				
Temporary pacemaker	66	73	100	100
Cardioversion	36	45	67	50
Cardiac massage	43	64	67	50
Potentially Life-Threatening Manifestations				
Temporary pacemaker	83	71	100	†
Cardioversion	25	14	0	†
Cardiac massage	8	14	0	†

*Group A = therapeutic/heart disease; group B = suicide/heart disease; group C = suicide/no heart disease; group D = accident/child/no heart disease.
†No children with less serious clinical manifestations required aggressive treatment in the postmarketing surveillance survey.
Sources: references 6 (patients 38 to 150) and 7.

numbers of these patients were insufficient in the postmarketing surveillance study, we took the data for this latter group from the pediatric patients in the multicenter trial.* Where experimental values are not available, such as for the patient outcomes without treatment with Fab fragments, parameter values are estimated based on all available information and expert judgment.

Table I presents the estimated probability of occurrence of each of the 3 disease outcome scenarios with and without treatment with Fab fragments for each patient group. The outcome estimates for the patients with manifestations of toxicity that are immediately life-threatening receiving symptomatic treatment only are based on the death rates for the arrhythmias most likely to occur in each patient group: ventricular tachyarrhythmias for those with heart disease,[8,9] and paroxysmal supraventricular tachycardia with heart block for those without heart disease.[10] No data exist on what the outcomes would have been in patients with less serious clinical manifestations without Fab treatment, and so our estimates are based on expert opinion. We do know that their physicians considered their symptoms to be potentially life-threatening and that their average serum digoxin levels were well above therapeutic levels. A higher probability of dying is always assumed for groups A and B than for groups C and D to account for deaths in these patients from their underlying heart disease in addition to deaths directly attributable to the digoxin toxicity.

Table II presents the probabilities of using temporary pacemakers, cardioversion and cardiac massage in patients who need aggressive therapy. Table III presents the average serum digoxin levels and number of vials of Fab fragments (40 mg/vial). The number of vials used varies according to the serum level of digoxin

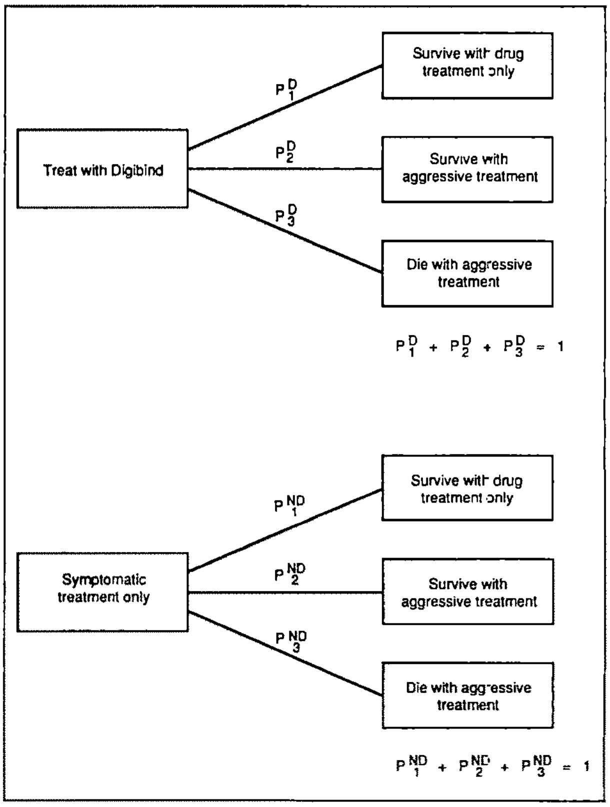
Treat with Digibind
P_1^D
P_2^D
P_3^D
Survive with drug treatment only
Survive with aggressive treatment
Die with aggressive treatment
$P_1^D + P_2^D + P_3^D = 1$
Symptomatic treatment only
P_1^{ND}
P_2^{ND}
P_3^{ND}
Survive with drug treatment only
Survive with aggressive treatment
Die with aggressive treatment
$P_1^{ND} + P_2^{ND} + P_3^{ND} = 1$

FIGURE 1. The 3 outcome scenarios for an episode of digoxin toxicity.

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*The data used from the multicenter trial included outcomes only for the children included among patients 38 through 150, because the earliest pediatric patients were not treated with Fab fragments until all alternative treatment methods had been tried.

TABLE III Mean Serum Digoxin Levels (ng/ml) and Mean Number of Vials (40 mg) of Fab Fragments Used

	Patient Groups*			
	A	B	C	D
Immediate Life-Threatening Manifestations				
Digoxin level	4.5	15.0	17.0	18.4
Number of vials	3.1	8.0	12.4	2.9
Days to <2.0 ng/ml for patients with average kidney function†	3.3	8.3	4.9	3.2
Potentially Life-Threatening Manifestations				
Digoxin level	5.0	9.0	10.0	13.1
Number of vials	2.8	7.7	7.1	1.5
Days to <2.0 ng/ml for patients with average kidney function†	3.8	6.2	3.7	2.7

*Group A = therapeutic/heart disease; group B = suicide/heart disease; group C = suicide/no heart disease; group D = accident/child/no heart disease.

†Estimated assuming exponential decay with a half-life of 1.6 and 1 day, respectively, for adults and children without heart disease, and 2.9 days for adults with heart disease (assuming an average creatinine clearance for these patients of 30 ml/min).

Sources: references 3, 6 (patients 38 to 150) and 7.

and the patient's weight as well as the physician's level of concern about the patient's clinical manifestations.

When Fab fragments are not given, a pharmacokinetic model[3] is used to estimate the time taken for serum digoxin levels to fall from the mean levels in each patient subgroup to the assumed toxic level, 2.0 ng/ml[11] (see Table III). This time was estimated based on the average calculated creatinine clearance for each patient subgroup. Normal renal function is assumed for patients without heart disease. Renal function is impaired for most patients with heart disease.[7,12] The average calculated creatinine clearance for patients with heart disease in the postmarketing surveillance study was 30 ml/min and was used to estimate the elimination half-life for these patients.

For those patients whose deaths are directly attributable to digoxin toxicity, death is assumed to occur within the first 48 hours, with an average stay of 1.67 days in intensive care (based on 1984 Medicare data). The use of Fab fragments is assumed to reduce the incidence of these early deaths only. For all patients not receiving Fab fragments, the time that it takes the serum digoxin level to decrease to <2.0 ng/ml is used to estimate the minimum time that the patient would spend in intensive care. Our estimates are consistent with data from Medicare patients with a primary diagnosis of digoxin toxicity in 1984 who had an average length of stay in intensive care of 3.4 days. When Fab fragments are given, the serum concentration of free digoxin decreases to undetectable levels within minutes and manifestations of toxicity resolve within 3 to 4 hours.[6,12] Therefore patients treated with Fab fragments are assumed to have a minimum stay of only 1 day in intensive care. An extra day in intensive care is assumed for all patients receiving aggressive therapy. Patients with prior heart disease are also assumed to remain an additional 1 day (if not treated with Fab fragments) or 2 days (if treated with Fab fragments) in intensive care to begin restabilization of their underlying heart disease.

After leaving intensive care, patients with heart disease are assumed to remain in routine care for 4 days for further restabilization (average length of stay for patients with arrhythmias or conduction disorders without complications and comorbidity [DRG 139] in North Carolina hospitals in 1988). Patients attempting suicide are also assumed to undergo inpatient psychiatric care for a total of 16 days after they leave intensive care (average length of stay for patients with depressive neuroses [DRG 426] in North Carolina hospitals in 1988). Restabilization of only 1 day of routine care is assumed for children with accidental ingestion.

Hospital resource cost data used were approximate values only, because these costs vary among hospitals. We assumed that the ratios of cost to charges for routine care days, intensive care days, and a temporary pacemaker were approximately 1. Charge data from a North Carolina hospital for these resources for 1990 were then used to approximate the costs of these resources. The average wholesale price of Digibind in September 1990 was used as the cost estimate for the Fab fragments. Changes in these costs do not change our cost-effectiveness estimates if their relative magnitudes remain approximately the same.

Cost-effectiveness estimates: The data presented in Tables I through III or previously described are used to compute net cost-effectiveness ratios for Fab fragments in the different patient groups. Table IV presents a

TABLE IV Summary of Benefits and Costs of Treatment with Fab Fragments in Four Patient Groups*

	A	B	C	D
Immediate Life-Threatening Clinical Manifestations				
Benefits				
Increased probability of survival†	0.39	0.37	0.50	0.40
Reduced medical care costs‡	n/a	n/a	n/a	$2,573
Costs				
Fab fragments§	$744	$1,920	$2,976	$696
Increased medical care costs‡	$2	$81	$65	n/a
Net costs	$746	$2,001	$3,041	($1,877)
Net cost/life-year saved‖	$1,912	$5,408	$169	<0
Potentially Life-Threatening Clinical Manifestations				
Benefits				
Increased probability of survival†	0.11	0.14	0.15	0.15
Reduced medical care cost‡	$2,060	$2,102	$1,949	$2,699
Costs				
Fab fragments§	$672	$1,848	$1,704	$360
Increased medical care costs‡	n/a	n/a	n/a	n/a
Net costs	($1,388)	($254)	($245)	($2,339)
Net cost/life-year saved‖	<0	<0	<0	<0

*Group A = therapeutic/heart disease; group B = suicide/heart disease; group C = suicide/no heart disease; group D = accident/child/no heart disease.

†From probabilities of dying in Table I.

‡Unit costs: cardiac care unit day = $1,000 including cardioversion and cardiac massage if needed; hospital day = $425; pacemaker = $1,500.

§Fab fragments (Digibind®) cost = $240 for 40 mg vial.

‖Assuming a remaining life expectancy for groups A and B, 1 year; C, 36 years; and D, 74 years.

n/a = not applicable.

summary of the estimated benefits and costs of treatment with Fab fragments. The benefits include an increased probability of survival for all patient groups. In addition, hospital costs per patient (excluding the cost of Fab fragments) are less for all children with accidental ingestion and for patient groups A, B and C with potentially life-threatening manifestations because of less need for aggressive therapy and shorter stays in intensive care for survivors. These overall hospital cost savings are achieved despite the fact that additional hospital costs are incurred for patients whose lives are saved because of using Fab fragments. They are also more than the additional cost of the Fab fragments and so the net costs of treating these patient groups are negative. For patient groups A, B and C with immediately life-threatening manifestations, the additional hospital costs for patients whose lives are saved are more than the reduced costs for survivors. Thus, the net costs of treating these patients, including the cost of the Fab fragments, are positive.

The results of our analysis are sensitive to changes in the assumed or estimated parameter values. In our study, the estimates of the net costs of treatment with Fab fragments are especially sensitive to the estimates of the magnitude of 2 effects of treatment: reduction in number of days in intensive care and reduction in probability of dying as a result of the toxic episode. The net costs of treatment with Fab fragments will be higher,

TABLE V Cost Per Increased Year of Life Associated with Reduced Risk of Death from Coronary Heart Disease or Stroke

Treatment	Cost Per Increased Year of Life
Fab fragments for digoxin toxicity in children and adults with potentially life-threatening manifestations	Negative costs
Fab fragments for digoxin toxicity in adults with therapeutic toxicity with immediately life-threatening manifestations	$1,900*
β-adrenergic antagonist therapy after MI in high-risk male patients aged 45 years[13]	$2,327†
Fab fragments for digoxin toxicity in adults with massive ingestion and immediately life-threatening manifestations	$5,400*
β blockers for hypertension for 52-year-old man[14]	$7,200‡
Simvastatin starting at age 35 years to lower serum cholesterol[15]	$23,000§
β-adrenergic antagonist therapy after myocardial infarction in low-risk male patients aged 45 years	$23,457‖
Heart transplant[16]	$23,500**
Simvastatin to lower serum cholesterol starting at age 60 years[15]	$49,000§
Coronary care unit versus intermediate level of care for patients (average age 60 years) with chest pain but at low risk for acute myocardial infarction[17]	$139,000

*Assuming underlying heart disease and a 1-year remaining life expectancy.

†Receiving 6 years of treatment and assuming 9 years continuing but decreasing effectiveness after end of treatment.

‡Assuming pretreatment systolic blood pressure of 180 mm Hg.

§For men with initial levels of 310 mg/dl.

‖Receiving 6 years of treatment and assuming no continuing effectiveness after end of treatment.

**No information on patient characteristics given.

Sources: references 13 to 17.

the smaller the reduction in intensive care days (by $1,000/day) because of the high cost of such care. The net costs of treatment with Fab fragments will also be higher, the larger the reduction in probability of dying because of the costs of treating additional survivors.

To compute the cost-effectiveness ratios, defined as cost per increased year of life expectancy, we assumed a remaining life expectancy of 1 year for patients with heart disease, 36 years for suicidal patients without heart disease. and 74 years for children. Under these assumptions, the cost per life-year saved ranges from negative for children and adults with potentially life-threatening manifestations to $5,400 for patients in group B with immediately life-threatening manifestations. These estimates are sensitive to our assumed outcome changes. For example, under the unlikely assumption that use of intensive care is not reduced at all by using Fab fragments, cost per life-year saved ranges from negative for children to a maximum of $23,000 for adults with massive ingestion.

DISCUSSION

The best way to estimate all the outcome changes attributable to a new treatment method is to measure the changes directly in a clinical trial that randomly assigns patients to the old and new treatment methods. Because Fab fragments are designed for use in life-threatening situations, no such trial has been performed. This study uses an alternative approach for comparing medical care use and health outcomes of comparable groups of patients treated with and without Fab fragments.

In this approach, we describe all the possible outcomes of an episode of digoxin toxicity and use available data to estimate the change in probabilities of these outcomes when treating with Fab fragments. We also estimate the resource use associated with each outcome. We have data to estimate the probabilities of the different outcomes when these patients are treated with Fab fragments. Although aggressive therapy was often instituted before Fab fragments were given and might be avoided by earlier administration, timing of treatment with Fab fragments is assumed, in this analysis, to be the same in general practice as was observed in the clinical studies. Because of the lack of experimental data, the probabilities of the different outcomes with symptomatic treatment only were estimated using information from the clinical literature and expert judgment about the specific patient mix in the treatment groups.

In general, net health care costs will be lowest for new treatments that reduce the use of health care resources that have high per-unit costs and that do not increase survival in the treated patients. Increased survival results in higher net costs. Where the net costs of a new treatment are positive, cost-effectiveness ratios provide good measures for the value of the drug. For those patients with immediately life-threatening manifestations treated with Fab fragments and for whom the net costs are positive, the cost per life-years saved ranged between $1,912 and $5,400. Compared with other treatments designed to increase life expectancy by reducing the risk of death from coronary heart disease, these costs per life saved for Fab fragments are small (see Table V). For example, in a recent study by Martens et al[15] of drugs designed to prevent cardiac disease through lower serum cholesterol levels, the cost per year of life saved for men with an initial serum cholesterol level of 310 mg/dl was estimated to be between $23,000 and $49,000 for simvastatin, a serum cholesterol-lower-ing drug, depending on the age when therapy was initiated. Thus, administering Fab fragments to patients with life-threatening digoxin toxicity could be considered quite cost-effective.

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Limitations of Testing Methods for Evaluation of Dual Chamber Versus Single Chamber Adaptive Rate Pacing

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As new modes of cardiac pacing are developed, it is important to determine if these modes offer additional benefits over already existing options. Comparisons between dual (DDDR) and single chamber ventricular (VVIR) rate-modulated pacing using standard exercise protocols have produced conflicting results.[1-4] Exercise duration alone does not appear to accurately reflect differences in cardiac efficiency and tissue perfusion. Similarly, maximal oxygen uptake tends to reflect exercise duration rather than cardiac performance.[5] This study was designed to compare the DDDR and VVIR pacing modes using measures of exercise duration and maximal oxygen uptake, as well as less frequently used parameters, including anaerobic threshold time, maximal carbon dioxide production, respiratory exchange ratio, cardiac output, and the ratio of cardiac output to oxygen uptake.

Fifteen patients (9 men and 6 women, age range 52 to 81 years [average 70]) with a normally functioning dual chamber adaptive rate pacemaker were studied. All patients were paced for symptomatic bradycardia; 13 had sick sinus syndrome and 4 had high-degree atrioventricular (AV) block. Ten patients had chronotropic incompetence and 3 had previously documented pacemaker syndrome associated with VVIR pacing (Table I). Patients were studied at rest and during

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TABLE I Individual Patient Data

Pt.	Mode	Age (yr) & Sex	Dx	ED/ Min	HR/ Max	METS	VO_2 Max	Ve/VO_2 Max	R Max	VCO_2 Max	AT Time	VO_2 at AT	O_2 Pulse	VO_2/ CO	CO Rest	CO Ex	CO Diff
1	DDDR	69F	CI, PS, SSS	10:22	137	5.02	1.39	38	1.09	1.52	8:30	1.13	10.15	0.10	6.06	13.3	7.24
1	VVIR			9:51	95	3.92	1.09	46	1.12	1.22	8:00	0.94	11.47	0.22	3.83	4.88	1.05
2	DDDR	78M	CI, PS, SSS	11:50	121	7.56	2.02	32.33	0.99	1.99	10:00	1.75	16.69	0.15	6.73	13.3	6.57
2	VVIR			11:48	126	—	2.20	35.58	0.80	1.77	9:30	1.70	17.46	0.36	3.63	6.17	2.54
3	DDDR	67M	CI, PS, SSS	11:50	121	7.35	2.01	32	1.06	2.17	11:50	1.85	16.86	0.18	6.07	11.10	5.03
3	VVIR			11:19	108	—	1.88	36	1.12	2.11	9:30	1.70	17.41	0.29	4.58	6.42	1.84
4	DDDR	76M	CI, PS, SSS	10:55	130	5.31	1.47	59.89	1.18	1.73	7:00	1.15	11.31	0.19	3.71	7.73	4.02
4	VVIR			8:07	132	—	1.44	69	0.81	1.17	6:00	1.14	10.91	0.23	4.08	5.53	1.45
5	DDDR	68M	CI, PS, SSS	11:34	120	6.11	2.28	39	1.10	2.50	9:00	1.68	19.00	0.26	4.56	8.76	4.20
5	VVIR			11:52	112	5.14	1.92	48	1.15	2.20	8:00	1.18	17.14	0.21	4.42	9.30	4.88
6	DDDR	75F	CI, SSS	11:00	128	4.69	0.89	51	0.97	0.86	0	0	6.95	0.16	2.37	5.47	3.10
6	VVIR			9:30	108	—	0.77	58	0.90	0.69	0	0	7.13	—	—	—	
7	DDDR	81F	SSS	7:04	120	4.09	0.81	38.67	1.01	0.82	6:40	0.77	6.75	0.10	4.17	8.40	4.23
7	VVIR			6:50	129	4.23	0.83	38.67	0.96	0.80	5:00	0.70	6.43	0.13	2.99	6.60	3.61
8	DDDR	68F	CI, PS, 3°	11:52	128	5.62	1.60	31.33	1.01	1.61	9:00	1.31	12.50	—	—	—	
8	VVIR			9:30	116	4.30	1.30	29.67	0.88	1.14	8:00	0.98	11.21	—	—	—	
9	DDDR	79F	SSS	9:52	115	4.49	1.01	32	0.99	1.00	7:30	0.86	8.78	—	—	—	
9	VVIR			8:45	114	4.73	0.98	32.67	0.97	0.95	7:30	0.96	8.60	—	—	—	
10	DDDR	69M	CI, 3°	12:56	110	7.18	2.39	33.3	1.17	2.80	5:30	1.10	21.73	—	—	—	
10	VVIR			10:59	140	5.74	1.91	27.67	1.04	1.99	5:00	1.20	13.64	—	—	—	
11	DDDR	52M	SSS	11:25	135	5.48	1.83	32.67	1.30	2.38	10:00	1.60	13.56	—	—	—	
11	VVIR			11:05	132	7.05	2.35	31.33	0.98	2.31	10:00	1.76	17.8	—	3.99	5.85	1.86
12	DDDR	68M	CI, PS, SSS, 2°	8:30	140	2.82	0.64	39	1.00	0.64	6:30	0.53	4.57	0.08	4.14	8.14	4.00
12	VVIR			7:51	137	3.03	0.69	44	0.99	0.68	6:30	0.58	5.04	0.14	2.24	5.07	2.83
13	DDDR	72M	SSS	12:51	121	6.69	2.01	42	1.06	2.14	6:00	1.00	16.61	0.18	5.44	11.39	5.95
13	VVIR			12:23	126	—	2.01	44.8	0.89	1.79	5:00	1.00	15.95	0.22	3.64	9.15	5.51
14	DDDR	72M	CI, SSS	17:02	140	—	2.26	37	0.86	1.95	14:45	1.79	16.74	0.16	4.45	13.73	9.28
14	VVIR			15:58	140	9.11	2.12	45	0.92	1.94	12:30	1.66	15.14	0.35	2.48	6.08	3.60
15	DDDR	71F	SSS	6:00	116	—	—	—	—	—	—	—	—	—	4.66	5.94	1.28
15	VVIR			5:00	114	—	—	—	—	—	—	—	—	—	4.04	5.17	1.13
% Impr	DDDR			10%	3%	7%	5%	7%	10%	16%	12%	7%	4%	63%	37%	48%	66%
p Score				NS	NS	NS	NS	NS	0.039	0.005	0.001	NS	NS	0.0028	<0.05	0.003	0.004

AT Time = time of anaerobic threshold; CI = chronotropic incompetence; CO Diff = change in cardiac output from rest to exercise (L/min); CO Ex = cardiac output at maximal exercise (L/min); CO Rest = cardiac output at rest (L/min); DDDR = dual chamber adaptive rate pacing; Dx = diagnosis; ED/Min = maximal exercise duration in minutes; HR/Max = maximal heart rate achieved; % Impr = percent improvement; METS = metabolic equivalents; NS = not significant; O_2 Pulse = oxygen pulse (oxygen uptake/heart rate); PS = pacemaker syndrome; R Max = maximal respiratory exchange ratio; SSS = sick sinus syndrome; VCO_2 Max = maximal carbon dioxide production; Ve/VO_2 = ventilatory equivalent for oxygen; VO_2 at AT = oxygen uptake at anaerobic threshold; VO_2/CO = oxygen uptake divided by cardiac output; VO_2 Max = ventricular adaptive rate pacing; VVIR = single chamber adaptive rate pacing; 2° = second-degree heart block; 3° = third-degree heart block; — = not obtained.

multistage treadmill exercise using the Chronotropic Assessment Exercise Protocol. Two exercise tests were performed, 1 in each pacing mode. The AV delay was programmed to that which had previously been determined as optimum for each patient at rest. In patients with Pacesetter Synchrony® pacemakers, the adaptive rate AV delay function was enabled during exercise. The use of adaptive rate AV delay with exercise is believed to be an important factor,[6–8] mimicking the progressive shortening of AV delay during exercise as seen in normal subjects.[9]

Pacing modes were randomly selected and blinded to the patient. Before enrollment in the study, all patients underwent ≥1 exercise test to familiarize them with the procedure. During the study, a symptom-limited maximal exercise test was performed in each mode allowing a minimum of 2 hours for recovery between tests. Exercise duration, heart rate, rhythm and metabolic equivalents were recorded while cardiac output and pulmonary gas exchange were measured. Cardiac output was measured by echo Doppler technique in a semisitting position at rest and immediately after exercise in each pacing mode. Stroke volume was determined from the flow velocity integral recorded with the Doppler sample volume positioned in the left ventricular outflow tract. Maximal values from pulmonary gas exchange were defined as the maximal values recorded during exercise. Anaerobic threshold was determined using a comparison of 3 established criteria.

It is recognized that some variability in exercise results exists with serial exercise testing. This effect was minimized by random assignment of pacing mode for each patient and by strict adherence to the treadmill protocol, as well as by prior familiarization of the patient with the exercise equipment.

Cardiac output determination by echo Doppler technique has been found to be reliable in measuring serial changes.[10-11] However, it is technologically difficult to perform this procedure during exercise, and its usefulness after maximal exercise is compromised owing to the problem of obtaining early determinations at equivalent times after exercise.

Pulmonary gas determination is influenced by multiple factors including variations in cardiac and pulmonary diseases. For this study, the effect on comparative changes in each patient was minimized, because the patient acted as his own control and the same variables were present for each test. Paced patients often exhibit a variety of rhythms in addition to their paced rhythm. In the VVIR mode, all patients were being paced at maximal exercise. Six patients had episodes of intrinsic or normal sinus rhythm, or both, during the early stages of exercise, but converted to a totally paced rhythm during the final stages of exercise. For each of these 6 patients, >70% of the total exercise time was in a totally paced rhythm. In the DDDR mode, all patients except 1 were being paced at maximal exercise. One patient showed atrial tracking with ventricular pacing, whereas the remaining 13 exhibited atrial and ventricular pacing. Three patients exhibited atrial tracking with ventricular pacing for up to 3 minutes of total exercise time. One patient developed an intrinsic rhythm during the final 30 seconds of exercise time. Four patients exhibited occasional atrial-tracked ventricular-paced beats during exercise.

Although there was a trend toward improved performance with DDDR pacing, analysis of exercise duration, maximal heart rate, metabolic equivalent, maximal oxygen uptake and oxygen pulse did not achieve statistical significance. Mean exercise duration was 10% greater with DDDR than with VVIR pacing. Maximal heart rate was 126 beats/min for DDDR and 122 for VVIR. Total metabolic equivalents achieved a 7% increase, whereas maximal oxygen uptake showed a 5% increase in the DDDR mode. The oxygen pulse showed a 4% increase, and oxygen uptake at anaerobic threshold had a 7% increase in the DDDR mode (Table I).

The values for maximal respiratory exchange ratio and carbon dioxide production, anaerobic threshold time and cardiac output reached statistical significance, suggesting that these parameters may be more powerful discriminators in the assessment of cardiac performance. Maximal respiratory exchange ratio showed a 10% increase, maximal carbon dioxide production a 16% increase and anaerobic threshold time a 12% increase. Cardiac output at maximal exercise showed a 48% increase in DDDR over VVIR (Table I), which is higher than that reported in other studies. The degree of improvement in cardiac output in this study appears to be related to several factors including exercise protocol (upright treadmill) and optimal AV delay programming with use of adaptive AV delay. The cardiac output difference, which is the difference between cardiac outputs at rest and during exercise, showed a 66% improvement with DDDR pacing over the increase associated with VVIR. Oxygen uptake divided by cardiac output is a measure correlating oxygen uptake with cardiac output; a lower ratio, indicating a higher cardiac output per given oxygen uptake, implies improved cardiac efficiency. This showed a 63% improvement with DDDR over VVIR. All measures related to cardiac output were the best parameters for the assessment of cardiac performance, although they were the most difficult to obtain (Table I).

It should be noted that the results of this study are affected by 7 of the 15 patients having overt pacemak-

er syndrome. Although 3 patients were known to have pacemaker syndrome before the study, pacemaker syndrome became apparent during the course of the study in the VVIR mode in an additional 4 patients. In the group with pacemaker syndrome, there was a 37% improvement in cardiac output at rest, a 64% improvement in cardiac output with exercise, and a 103% improvement in cardiac output difference when comparing DDDR with VVIR. For the group who did not manifest pacemaker syndrome, improvement in cardiac output with exercise was 43% and that in cardiac difference was 48%. Although the results of this study are influenced by the large percentage of patients with pacemaker syndrome, this may be an accurate representation of the general population, because pacemaker syndrome occurs more often than previously believed; some recent studies reported its incidence to be as great as 83%.[12-14]

Patients in this study showed better performance in the DDDR than in the VVIR mode. Though the degree of improvement for each parameter varied and not all achieved statistical significance, there was a consistent trend toward DDDR pacing. Those measurements in which a statistically significant difference was identified include cardiac output, anaerobic threshold time, oxygen uptake at anaerobic threshold, and maximal carbon dioxide production and respiratory exchange ratio. Exercise duration and measurements that are closely associated with it appeared to be relatively poor discriminators between pacing modes with respect to cardiac performance. This study indicates that an evaluation comparing the effect of 1 pacing mode with another with regard to cardiac function is best accomplished using multiple parameters. Except for cardiac output, which is the most difficult to measure, no other single parameter adequately reflects the hemodynamic differences between DDDR and VVIR pacing in all patients.

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Usefulness of Coronary Angiography in Patients Requiring Repeat Cardiac Valve Surgery

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Widespread application of surgical treatment for valvular heart disease has made the diagnosis of prosthetic valve dysfunction of great clinical importance. Recent advances in cardiac imaging techniques, including color Doppler and transesophageal echocardiography, provide such a detailed picture of valve anatomy and function that often cardiac catheterization adds little to the assessment.[1,2] Despite adequate noninvasive assessment of prosthetic valve function, adult patients continue to undergo cardiac catheterization before reoperation to rule out the development of new significant coronary artery disease. This is usually performed even if the patient has been shown to be free of coronary artery disease at the time of initial valve surgery. The frequency with which significant coronary artery disease develops or progresses in patients with valvular heart disease and the diagnostic yield of repeat coronary arteriography have not been adequately defined. This study examines a consecutive series of patients with prosthetic heart valves who underwent cardiac catheterization for recurrent symptoms to determine (1) the frequency with which new significant coronary disease de-

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TABLE I Characteristics of Group 1 Patients Without and Group 2 Patients With Significant Coronary Artery Disease at Initial Catheterization

	Group 1 (n = 75)	Group 2 (n = 15)	p Value
Age (years)	49 ± 13	65 ± 8	0.001
Number of men	16 (21%)	11 (73%)	0.001
Aortic valve disease	26 (33%)	10 (67%)	0.02
Progression of CAD	7 (9%)	9 (60%)	0.001
Time since surgery (years)	11 ± 10	8 ± 5	NS

CAD = coronary artery disease; NS = not significant.

TABLE II Group 1 Patients With and Without New Significant Coronary Artery Disease

	New CAD (n = 7)	No CAD (n = 68)	p Value
Number of men	3 (43%)	13 (19%)	NS
Age (years)	55 ± 13	49 ± 13	NS
Aortic valve surgery	3 (43%)	22 (32%)	NS
Time since surgery (years)	12.5 ± 5.1	8.0 ± 5.3	0.08
Angina/myocardial infarction	6 (86%)	12 (18%)	0.001

CAD = coronary artery disease; NS = not significant.

velops in patients without previous disease, (2) the frequency with which new significant lesions appear in patients with known disease, and (3) clinical parameters that may identify patients with new significant coronary artery disease.

The angiography reports and medical records of all adult patients with a history of valve surgery who underwent cardiac catheterization for symptoms of valve dysfunction or angina at The University of North Carolina Hospitals between January 1986 and December 1990 were reviewed. Significant coronary artery disease was defined as ≥50% stenosis in at least 1 coronary artery visually estimated by an experienced angiographer. Progression of disease was considered to be the development of a new ≥50% stenosis or occlusion of a vessel or bypass graft. Angina was defined as a history of chest pain interpreted as ischemia and myocardial infarction was defined by a history of typical symptoms accompanied by characteristic cardiac enzyme or electrocardiographic changes, or both.

Patients were divided into 2 groups based on absence (group 1) or presence (group 2) of significant coronary artery disease on the initial catheterization. Differences between groups were compared using a 2-tailed t *test for continuous variables and Pearson's chi-square method for categorical variables. Data are presented as mean ± standard deviation with a p value <0.05 considered significant.*

The study group consisted of 90 patients whose baseline characteristics are listed in Table I. Group 2 patients with coronary artery disease were older (p = 0.001) men (p = 0.001), and more often had aortic valve disease (p = 0.02). The 75 group 1 patients were restudied after a mean interval of 11.0 ± 10.4 years (Table II). Only 7 of these 75 patients (9%) developed new significant coronary artery disease. One-vessel disease developed in 3 patients, 2-vessel disease in 3 patients, and 1 patient had an angiographically documented thrombus extending from the prosthetic valve ring into the left main coronary artery. The interval between surgery and second catheterization in patients with and without new significant coronary artery disease was similar (12.5 ± 5.1 vs 8.0 ± 5.3 years, p = not significant).

New significant coronary disease occurred more often in older male patients, and those with aortic valve disease, but because of the small number of patients developing new coronary artery disease the differences were not statistically significant. An interval history of angina or myocardial infarction was found in 6 of these 7 group 1 patients. Only 1 patient in group 1 was found to have significant coronary artery disease (a 70% mid-left anterior descending stenosis) without a history of angina or myocardial infarction. Ten patients with a history of angina and 2 patients with a history of myocardial infarction did not have new significant coronary artery disease.

In group 2, 10 of 15 patients underwent coronary artery bypass graft surgery in addition to the initial valve surgery. During a mean follow up of 8.3 ± 5.4 years, 9 of 15 patients (60%) had progression of coronary artery disease.

Patients with valvular heart disease requiring surgery often undergo coronary arteriography to determine the need for concomitant coronary artery bypass grafting. Previous studies of patients being evaluated before their first valve operation have attempted to use clinical characteristics to identify those who are at low risk for coronary artery disease, and obviate the need for coronary arteriography.[3-5] No previous studies have examined the need for coronary angiography in patients with valvular heart disease whose coronary artery disease status is already known, although several years previously. Serial angiographic studies of patients with no coronary artery disease suggest that in the presence of persistent or recurrent anginal symptoms, approximately 15% of the patients have new coronary artery disease when restudied after 1 to 13 years.[6-8] Patients with mild disease (<50% stenosis) have a higher rate of disease progression compared to that of patients with no coronary artery disease.[7-10]

This study was designed to determine the likelihood of adult patients developing coronary artery disease after heart valve surgery. In this study as well as in others,[3-5] older men with aortic valve disease were more likely to have coronary artery disease initially. Only 7 of 75 (9%)

patients without significant coronary disease at the initial catheterization developed disease over a mean interval of 12.5 ± 5.1 years, and 6 (86%) were identified by the interim development of angina or myocardial infarction. Although these patients tended to be older men with aortic valve disease, this trend was not statistically significant. If angina or myocardial infarction were used to determine the need for repeat coronary arteriography, only 18 of 75 patients (24%) would undergo arteriography and 6 would be found to have new coronary disease. Repeat coronary arteriography could have been avoided in 57 of 75 patients (76%) at a cost of missing 1 patient with new 1-vessel disease. The low yield of coronary arteriography in group 1 patients is not unexpected. Group 1 patients were women (79%) (mean age 49 years), a group with an approximately 5 to 10% likelihood of having coronary disease in the absence of typical angina.[11] Furthermore, the significance of undiagnosed coronary disease in an asymptomatic patient is debatable, because the benefit of adding empiric revascularization to valve surgery in such patients is not clearly established.[12]

In contrast to the findings in group 1, 60% of patients in group 2 with preexisting coronary disease developed additional disease when restudied. It is therefore reasonable to assume that repeat coronary arteriography is indicated in all patients with prior valve surgery and known coronary artery disease.

Because this is a retrospective study, coronary disease risk factors could not be accurately assessed in all patients. Other noninvasive methods such as exercise stress tests for detecting coronary disease were not uniformly applied. Such additional information may further help in identifying patients at very low risk for developing new coronary artery lesions.

Adult patients who undergo valve surgery and are free of significant coronary artery disease appear to have a very low likelihood of developing new significant coronary artery disease when restudied for symptoms of valve dysfunction. The few patients who developed new significant coronary artery lesions can be identified by clinical criteria. Therefore, since information concerning ventricular and valve function and valve anatomy can be obtained noninvasively, most patients known to be free of coronary disease initially can safely be spared the added risk and expense of repeat coronary arteriography.

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Effectiveness of Balloon Percutaneous Valvuloplasty for Stenotic Bioprosthetic Valves in Different Positions

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Percutaneous balloon valvuloplasty has been used as treatment for native valvular stenosis in the mitral, aortic, pulmonary and tricuspid positions.[1–4] It has also been used as palliative therapy for stenotic bioprosthetic valves.[5–8] In this study we present the immediate results and midterm follow up of percutaneous balloon valvuloplasty of 5 bioprosthetic valves in different positions.

Percutaneous balloon valvuloplasty was performed in 5 patients who had stenotic porcine bioprosthetic valves. Three of them were in mitral, 1 in aortic and 1 in the pulmonic position. Sizes ranged from 25

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TABLE I Clinical and Functional Data

Case	Valve Position	Model	Size	EBA	IP (yrs)	Gradient (mm Hg)		Area (cm^2)		VR		Follow-Up (mos)
						B	P	B	P	B	P	
1	Mitral	Hancock	31	3.8	10	15	11	1.1	1.4	I	IV	12
2	Mitral	Carpentier	29	3.8	3	13	3	1.3	2.5	0	0	12
3	Mitral	Carpentier	29	4.9	7	16	5	0.9	1.7	0	0	7
4	Aortic	Carpentier	25	3.1	8	60	40	0.8	0.9	I	III	17
5	Pulmonic	Hancock	25	1.8	12	70	50	—	—	I	I	6

B = basal; EBA = effective balloon area; IP = valve implanted period; P = postdilatation; VR = valve regurgitation.

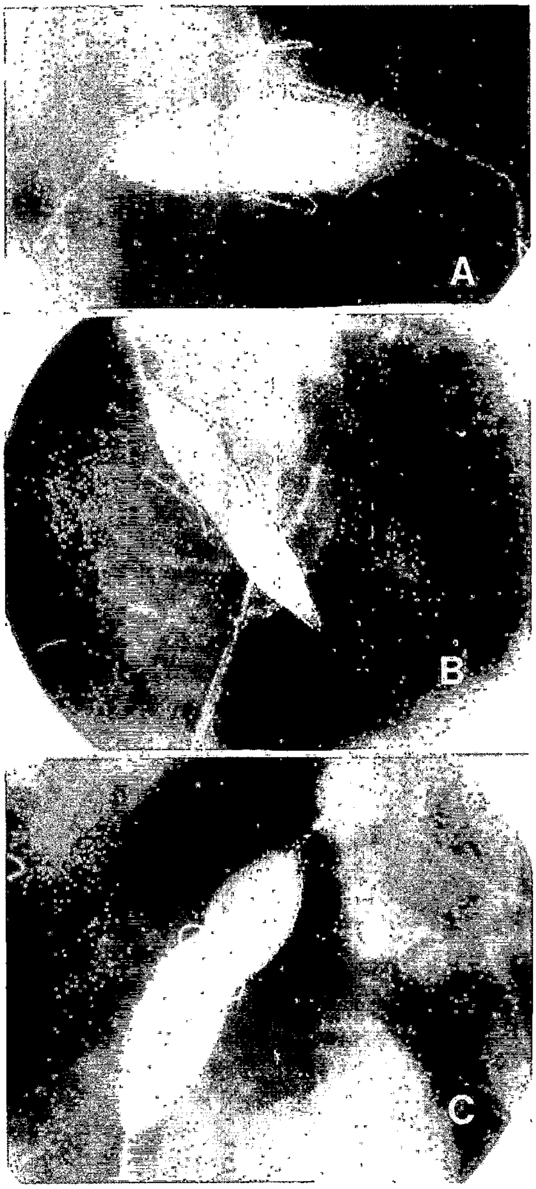

FIGURE 1. *A*, right anterior oblique projection showing a 25 mm monoballoon inflated through a Carpentier-Edwards mitral bioprosthetic valve. *B*, a 20 mm monoballoon inflated through a Carpentier-Edwards prosthesis in aortic position. *C*, the left anterior oblique projection showing a 15 mm monoballoon catheter inflated through a Hancock prosthesis in the pulmonary position.

to 31 (Table I). These valves were in place for $>$7 years, except in 1 patient with a mitral prostheses in which stenosis appeared 3 years after implantation. All patients were in New York Heart Association functional class II to III. Echocardiographic studies showed valve calcium with conservated cusp mobility in all patients except patient 2, in whom we observed only a moderate fibrosis. Echo-Doppler functional studies were performed in the basal state, 72 hours after the procedure, and every 3 months during a mean follow-up of 10 ± 3 months (range 6 to 14). Percutaneous balloon valvuloplasty in the mitral position was performed through an anterograde access using a 25 mm trefoil balloon in 2 patients, and a 25 mm monoballoon in the third (Figure 1A). Dilatation in the aortic position was done through arterial retrograde access with a 20 mm monoballoon (Figure 1B). A 15 mm monoballoon catheter was also used in the pulmonary position (Figure 1C). In the first patient with mitral percutaneous balloon valvuloplasty, the pressure gradient decreased from 15 to 11 mm Hg and the functional mitral valve area increased from 1.1 to 1.4 cm^2 after balloon dilatation. Postprocedural left ventriculography showed an increase in mitral regurgitation from grade 1 to 2/4. After a slight clinical improvement, the patient developed a poor functional condition as the valve regurgitation increased progressively. Echocardiographic study showed a moderate mitral regurgitation at 6-month follow-up and a clear cusp rupture with severe regurgitation on the 12th month. The patient died during hospital admission because of ventricular arrhythmia. The second patient had a mitral gradient reduction from 13 to 3 mm Hg, with a functional valve area increase from 1.3 to 2.5 cm^2. No immediate mitral regurgitation was observed. The third patient had a gradient reduction from 16 to 5 mm Hg and an increase in mitral valve area from 0.9 to 1.7 cm^2 with no valve regurgitation. In both patients 2 and 3, no regurgitation was seen at follow-up. However, restenosis was observed by Echo-Doppler 6 to 7 months after the procedure, registering *valve areas of 1.3 and 1.1 cm^2, respectively; both underwent repeat operation. In the patient with percutaneous balloon valvuloplasty in the aortic position, the systolic pressure gradient decreased from 60 to 40 mm Hg, with an aortic valve area increase of 0.84 to 0.90 cm^2. An aortic regurgitation grade 1/4 appeared after dilatation, increasing progressively to grade 3/4 after 12 months. The patient underwent repeat operation 14 months after balloon dilatation, confirming a bioprosthesis cusp rupture. The patient with a percutaneous balloon valvuloplasty in the pulmonary position had a basal systolic gradient of 70 mm Hg that decreased to 45 mm Hg after dilatation. There was an increase in basal regurgitation from grade 1 to 2/4. This patient also had a muscular ventricular septal defect with equalization of ventricular pressures. After percutaneous balloon valvuloplasty dilatation, the ventricular defect became restrictive, showing an interventricular left to right shunt of 25 mm Hg. The clinical condition and echocardiographic parameters of the patient did not modify 6 months after the procedure.*

This brief review shows the variability of the initial results of the procedure, and the poor outcome of bioprosthetic valve dilatation at midterm follow-up. Therefore, this procedure should be considered as a short-term palliative therapy restricted to a small subgroup of patients: those in critical situations who need stabilization before surgery, patients with early bioprosthesis stenosis with fine and mobile cusps, and those with a bioprosthesis implanted in the right side of the heart where a valvular regurgitation will be better tolerated.

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Clinical Spectrum of Venous Thrombi in the Fontan Patient

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Venous thrombus formation is a known complication after the Fontan procedure. To characterize the clinical presentation, diagnostic methods, treatment regimens and outcome of this disease process, we retrospectively reviewed the records of 7 patients who developed systemic venous or pulmonary arterial thrombosis after modifications of the Fontan operation. Clinical features were analyzed to identify "risk factors" that may predispose to thrombus formation.

From April 1981 to May 1991, 64 patients have undergone the Fontan procedure or one of its modifications at the Medical University of South Carolina. Postoperatively, thrombi have been detected in 6 of 64 patients. A seventh patient who underwent the Fontan operation at another institution developed a thrombus during follow-up at our institution. These 7 patients ranged in age from 6 months to 18 years. All were found to have systemic venous or pulmonary artery thrombi. Thrombi were detected in multiple locations including the inferior vena cava–baffle anastomosis, within the baffle, right atrium and pulmonary artery. Two subgroups have been identified based on time interval between Fontan operation and thrombus detection.

The "early" subgroup (patients 1, 2, 3 and 4 [Table I]) presented 1 day to 11 months (median 16 days) after the Fontan procedure. All patients in this subgroup were critically ill at time of thrombus detection. Thrombus formation was diagnosed by angiography in 2 patients and by transesophageal echocardiography in the other 2. Despite aggressive thrombolytic and anticoagulation measures with streptokinase and heparin along with surgical revision of the operation, 3 of 4 early presenters had recurrent thrombi detected. Outcome was poor in all; 3 patients died and the fourth is left with a static encephalopathy.

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TABLE I Clinical Characteristics

Pt. No.	Age (years)	Time After Fontan	Low CO	Resp. Distress	Low O_2 Sat.	Diagnostic Modality	Thrombus Location	Central Line	Pacing Wires	Outcome
1	0.5	1 day	0	+	+	Angiography	RPA	+	0	Died
2	2	2 days	+	0	0	TEE	IVC-RA/RA-PA	+	0	Encephalopathy
3	3.5	1 mo	+	+	+	TEE	RA	+	0	Died
4	6	11 mos	+	+	+	Angiography	RPA	+	0	Died
5	10	5 years	0	0	0	TEE	RA	0	+	Organized
6	14	4 years	0	0	0	TEE	RA	0	+	Resolved
7	18	7 years	0	0	0	Surface echo	RA	0	0	Resolved

CO = cardiac output; IVC = inferior vena cava; O_2 Sat. = oxygen saturation; PA = pulmonary artery; RA = right atrium; Resp. = respiratory; RPA = right pulmonary artery; TEE = transesophageal echocardiogram; + = present; 0 = absent.

The "late" subgroup (patients 5, 6 and 7 [Table I]) presented 4 to 7 years (median 5) after the modified Fontan operation. Patients who presented late after Fontan operations were not in critical distress at the time of thrombus detection. One presented with transient dysarthria and paralysis, the second with atrial flutter, and the third was asymptomatic. Thrombus was detected by surface echocardiography in 1 patient and by transesophageal echocardiography in the other 2. All 3 patients were treated with warfarin with resolution or organization of thrombi.

Irrespective of time from operation to thrombus discovery, additional factors were present in our study group that appeared to place them at "risk" for thrombosis. All but 1 of our patients had at least 1 risk factor, and 5 of 7 had multiple risk factors. Factors included: central venous lines, 4 of 7; low cardiac output states, 3 of 7; hyproteinemia, 3 of 7; intracardiac pacing wires, 2 of 7; dysrhythmia, 2 of 7; atrial baffle narrowing or obstruction, 1 of 7; and a thrombolytic abnormality, 1 of 7.

The formation of thrombi in the systemic venous circulation is a known complication of the Fontan procedure.[1–3] These may occur due to low-velocity flow states in the absence of a right-sided pump mechanism. Additional risk factors for venous thrombi may be identified in patients who have this postoperative complication.

The clinical presentation of the Fontan patient with systemic venous thrombi is diverse. Two subgroups of patients are apparent. Despite maximal medical and surgical management all patients who presented early had a poor outcome. Those who presented late have shown resolution of thrombosis using oral anticoagulation therapy. An attempt to further define clinical subgroups from published reports is hampered by small patient numbers, but similar cases of poor outcome in "early presenters" are found.[1,2] There does appear to be a high mortality associated with reoperation.

Thrombus formation after the Fontan operation has been reported as rare; however, we report this complication in 6 of 64 patients who have undergone variations of the Fontan procedure at our institution. The true prevalence of thrombi in these patients may be higher than previously suspected as indicated by findings of transesophageal echocardiographic studies.[4] Physicians managing patients after the Fontan procedure should maintain a high level of concern regarding thrombus formation, especially if additional risk factors are present.

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Clinical Characteristics of Patients with Acute Pulmonary Embolism

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Among 117 patients with pulmonary embolism (PE) and no prior cardiac or pulmonary disease who participated in the National Heart, Lung, and Blood Institute Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, combinations of clinical characteristics were identified that were present in nearly all in whom the diagnosis of PE was made.[1] We now assess these as well as additional combinations of characteristics in the entire population of patients with acute PE who participated in PIOPED, irrespective of the presence of prior cardiopulmonary disease.

The eligible population consisted of patients aged ≥18 years in whom acute PE was of diagnostic concern. Symptoms suggestive of PE were required within 24 hours of entry into the study.[2] The PIOPED study consisted of 2 groups. In 1 group, patients who consented to participate in the investigation were obligated to undergo pulmonary angiography if their ventilation/perfusion scans were abnormal. There were 251 patients with acute PE in this arm of the PIOPED study in whom the diagnosis was made by angiography.[2] There was a second group in the PIOPED study which was not described in the PIOPED report. This group included patients who by random sample were not selected for sensitivity and specificity analyses of their ventilation/perfusion scans, and who, therefore, were not obligated by protocol to undergo angiography if their ventilation/perfusion scans were abnormal. Also in this group were patients who refused mandatory angiography and, therefore, refused to participate in the first arm of the study. However, many of these patients underwent diagnostic angiography at the request of their attending physicians. There were 132 patients in this arm of the study who had PE diagnosed by angiography. The present investigation reports the clinical characteristics of acute PE in the 383 patients with acute PE who were in either arm of the PIOPED study. Comparisons were made with 843 patients in whom suspected PE was excluded, either by angiography (677 patients) or follow-up and outcome classification (166 patients). The method of outcome classification has been described.[2]

Chest radiographs were obtained within 24 hours of angiography in all patients. The partial pressure of oxygen in arterial blood (PaO_2), with the patient breathing room air, was measured within 24 hours before the diagnostic pulmonary angiogram in 280 patients with and 624 patients without PE. Detailed methods have been reported.[2]

A chi-square with Yates' correction was used to compare the prevalence and distribution of clinical features. Because of the large number of comparisons made in this analysis, p values tend to exaggerate the statistical significance of observed differences. Comparisons of continuous variables were made with a Student's t test. Data were analyzed at the Henry Ford Heart and Vascular Institute from a tape provided by the PIOPED Data and Coordinating Center. The patients with acute PE were 58 ± 17 years of age (mean ± standard deviation); 204 were men (53%). Patients in whom PE was excluded were 55 ± 18 years of age; 355 (42%) were men. Among the 383 patients with acute PE the most frequent symptoms were dyspnea in 299 (78%), pleuritic pain in 225 (59%) and cough in 166 (43%). The most frequent signs of PE were tachypnea (respiratory rate ≥20 beats/min) in 278 (73%), rales in 210 (55%) and tachycardia (heart rate >100 beats/min) in 115 (30%). The frequency of symptoms and signs in 843 patients with no PE was not significantly different. The most frequent radiographic abnormality was atelectasis or a pulmonary parenchymal abnormality, either or both of which were observed in 263 patients (69%) with and 483 (58%) without PE ($p < 0.001$). A pleural effusion was present in 180 (47%) with and in 327 (39%) without PE ($p < 0.01$). A pleural-based opacity was present in 132 (34%) with and 223 (26%) without PE ($p < 0.01$). An elevated diaphragm was present in 106 (28%) with and in 175 (21%) without PE ($p < 0.01$). The PaO_2 while breathing room air was <80 mm Hg in 226 of 280 (81%) with and 458 of 624 (73%) without PE ($p < 0.05$).

Combinations of signs, symptoms, radiographic features and PaO2 most frequently present in patients with PE are listed in Table I. These combinations of clinical characteristics occurred with nearly the same frequency (within 1%) among patients in whom PE was excluded.

Combinations of signs and symptoms associated with PE in patients with no prior cardiopulmonary disease

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TABLE I Combinations of Clinical Findings in Patients with Acute Pulmonary Embolism

	No. of Pts. (%)
Dyspnea or tachypnea*	347/383 (91)
Dyspnea, tachypnea or pleuritic pain	371/383 (97)
Dyspnea, tachypnea, pleuritic pain or DVT	373/383 (97)
Dyspnea, tachypnea, pleuritic pain, or x-ray atelectasis/parenchymal	379/383 (99)
Dyspnea, tachypnea, pleuritic pain, DVT or x-ray atelectasis/parenchymal	381/383 (99)
Dyspnea, tachypnea, pleuritic pain, DVT, x-ray atelectasis/parenchymal or PaO2 <80 mm Hg	280/280 (100)

*Tachypnea = respiratory rate ≥20 beats/min.
DVT = signs of deep venous thrombosis; PaO_2 = partial pressure of oxygen in arterial blood.

were identified among patients who participated in the Urokinase Pulmonary Embolism trial,[3] and this experience was expanded upon in the PIOPED study through the identification of additional useful combinations.[1] Although such combinations are not specific for PE, they are extremely sensitive in identifying the population in whom PE should be considered. In the present study we tested combinations of clinical characteristics among all patients with acute PE, irrespective of prior cardiopulmonary disease Several combinations were present in almost all patients with acute PE. Dyspnea or tachypnea or pleuritic pain or radiographic evidence of atelectasis or a parenchymal abnormality occurred in 99% of patients. All patients with PE had dyspnea or tachypnea or pleuritic pain or deep venous thrombosis or atelectasis/parenchymal abnormality or a PaO2 <80 mm Hg. These data indicate that among patients in whom PE was identified, only a small percentage did not have a number of important manifestations. These manifestations are not specific for PE, and their presence does not necessarily warrant initiation of an investigation for PE. However, the recognition of these manifestations assists in identifying patients in whom ventilation/perfusion scans or angiography, or both, may be necessary.

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Lymphoproliferative Disorder Early After Cardiac Transplantation

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In cardiac transplantation, extremely potent immunosuppressive agents are used, which leave the host vulnerable to a variety of infections and malignancies. Among the malignancies, lymphoproliferative disorders are the most common.[1] Most cases of posttransplant lymphoproliferative disorders have been described in patients who have undergone several months of immunosuppression.[2,3] This report describes our experience with patients who developed lymphoproliferative disorder within 3 months of heart transplantation.

Our patient population includes all patients who underwent cardiac transplantation at the University of South Florida/Tampa General Hospital and at St. Joseph's Hospital in Tampa, Florida. As of December 1989, 79 patients had undergone heart transplantation at University of South Florida/Tampa General Hospital and 13 at St. Joseph's Hospital. All patients received immunosuppressive therapy with cyclosporine, azathioprine and prednisone in doses adjusted to the overall clinical condition. In addition, during 1989, "induction" or prophylactic immunosuppressive therapy with OKT3 was initiated within 48 hours of cardiac transplantation. OKT3 was administered by an intravenous infusion of 5 mg/day for 14 consecutive days.

We defined lymphoproliferative disorder as a histologically documented disorder characterized by uncontrolled monoclonal or polyclonal proliferation of B lymphocytes within, or separate from, lymph nodes. Clinical data were obtained from individual medical records.

Table I outlines the salient features in our patients with lymphoproliferative disorder. All patients received OKT3, 3 as part of a prophylactic "induction" protocol and 2 as rescue therapy for acute early cardiac rejection unresponsive to high-dose intravenous corticosteroid therapy. The initial clinical presentation included fever, lymphadenopathy and abnormal liver function tests. In 3 patients the clinical course was one of rapid irreversible multisystem failure and at autopsy all 3 patients with active lymphoprolifera-

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TABLE I Clinical Features of Five Patients with Lymphoproliferative Disorder Early After Transplantation

Pt. No.	Age (yr) & Sex	Total OKT3 Dose (mg)	Interval (wks)	Fever	Abnormal LFT	PTL Type	Organ Involved
1	53M	70–I	5	+	+	Polyclonal	LN, LVR, PCRD, kidney, adrenal
2	34M	70–I	3	0	0		LN, LVR, SP
3	51M	70–R	9	+	0	Polyclonal	LN, heart
4	59M	70–R	12	+	+	Polyclonal	LN, LVR, SP, PCRD, colon, adrenal, bone marrow
5	65M	70–I	10	+	0		LN, LVR, SP, PCRD, pleura, kidney, urinary bladder

I = prophylactic "induction" therapy; Interval = time in weeks from heart transplant to onset of lymphoma; LFT = liver function test; LN = lymph node; LVR = liver; PCRD = pericardium; PTL = post-transplant lymphoproliferative disorder; R = rescue therapy; SP = spleen; 0 = absent; + = present.

tive disorder had diffuse multiorgan involvement. Patient 2 died of acute severe graft rejection and the lymphoproliferative disorder was an unsuspected finding. Patient 3, who had his immunosuppressive therapy decreased, died of coronary vasculopathy without evidence of active lymphoproliferative disorder.

The reported incidence of lymphoproliferative disorder in transplant patients is approximately 2%.[1] The higher reported incidence of lymphoproliferative disorder in heart transplant patients has been attributed to the high level of immunosuppression to which these patients are subjected.[4] In our patient population, the incidence of lymphoproliferative disorder is approximately 5.5%.

Post-transplant lymphoproliferative disorders have been associated with Epstein-Barr virus infection.[5,6] In the nonimmunosuppressed host, Epstein-Barr virus stimulates B-cell proliferation which is usually kept in check by immune regulatory mechanisms, specifically the cytotoxic T lymphocytes. It is proposed that in transplant patients, immunosuppression allows for the uncontrolled proliferation of B lymphocytes.[1] Not all transplant patients who are infected with Epstein-Barr virus develop lymphoproliferative disorder. Some investigators have suggested that primary Epstein-Barr virus infection, reactivation of Epstein-Barr virus during profound immunosuppression and possibly high antigenic stimulation from the graft may be factors contributing to the development of lymphoproliferative disorder.[1,4,5]

OKT3, a monoclonal antibody that binds to the CD3 antigen present on T cells, causes paralysis of the T cells and inhibits cytotoxic T-cell function. Although useful in reversing acute cellular rejection, OKT3 may be a factor contributing to the development of lymphoproliferative disorder. A similar experience to ours has been reported by the cardiac transplant group at Loyola University.[6] In both series, patients with early lymphoproliferative disorder presented with fever and fulminant multiorgan involvement, which appeared to be related to the use of OKT3. The relation with OKT3 may have geographical variability because, in other transplant programs, the use of OKT3 does not seem to predispose patients to lymphoproliferative disorder (O'Connell JB, personal communication).

Early lymphoproliferative disorder presents as a febrile, disseminated multisystem disease that can be rapidly fatal. There appears to be a relation between the use of OKT3 and the appearance of early lymphoproliferative disorder. The risks and benefits of early aggressive antithymocyte therapy should be carefully assessed.

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Appearance of or Persistence of Severe Mitral Regurgitation Without Left Ventricular Outflow Obstruction After Partial Ventricular Septal Myotomy-Myectomy in Hypertrophic Cardiomyopathy

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At the National Heart, Lung, and Blood Institute from 1959 through October 1989, 626 patients underwent operative treatment of obstructive hypertrophic cardiomyopathy: ventricular septal myotomy-partial myectomy alone in 539 patients; mitral valve replacement alone in 68 patients; and both procedures, not necessarily simultaneously, in 27 patients. The septal myotomy-myectomy procedure in most patients provided clinical improvement, but in some patients the results of this procedure have been unsatisfactory and reoperation has been performed.[1] In the 27 patients who underwent reoperation after septal myotomy-myectomy, the indication was persistent left ventricular outflow obstruction in 24 patients[2] and pure mitral regurgitation, without outflow obstruction, in 3 patients. This report describes certain clinical and morphologic features in the latter 3 patients.

Certain clinical and operative findings in the 3 patients are summarized in Table I. All 3 patients had peak systolic pressure gradients at rest or with provocation between left ventricle and systemic artery >50 mm Hg before the myotomy-myectomy operation, and 1 patient (no. 2) had a large (61 mm Hg) gradient across the right ventricular outflow tract. All 3 patients also had mitral regurgitation before the myotomy-myectomy operation performed through an aortotomy. Mitral regurgitation in patient 1 was only mild before the myotomy-myectomy operation but severe afterwards; in patient 2, mitral regurgitation was severe both before and after the initial operation (Figure 1), and in patient 3 it was of moderate degree before myotomy-myectomy and severe afterwards. All 3 patients had complete relief of left ventricular outflow obstruction by the myotomy-myectomy operation; nevertheless, severe symptoms of cardiac dysfunction persisted. At reoperation, ruptured mitral chordae tendineae were found in patients 1 and 2 and severe posterior mitral leaflet systolic anterior motion in patient 3. In none of the 3 patients was the mitral anulus dilated. The operatively excised mitral valves are shown in Figure 2. After mitral replacement, symptoms of cardiac dysfunction less-

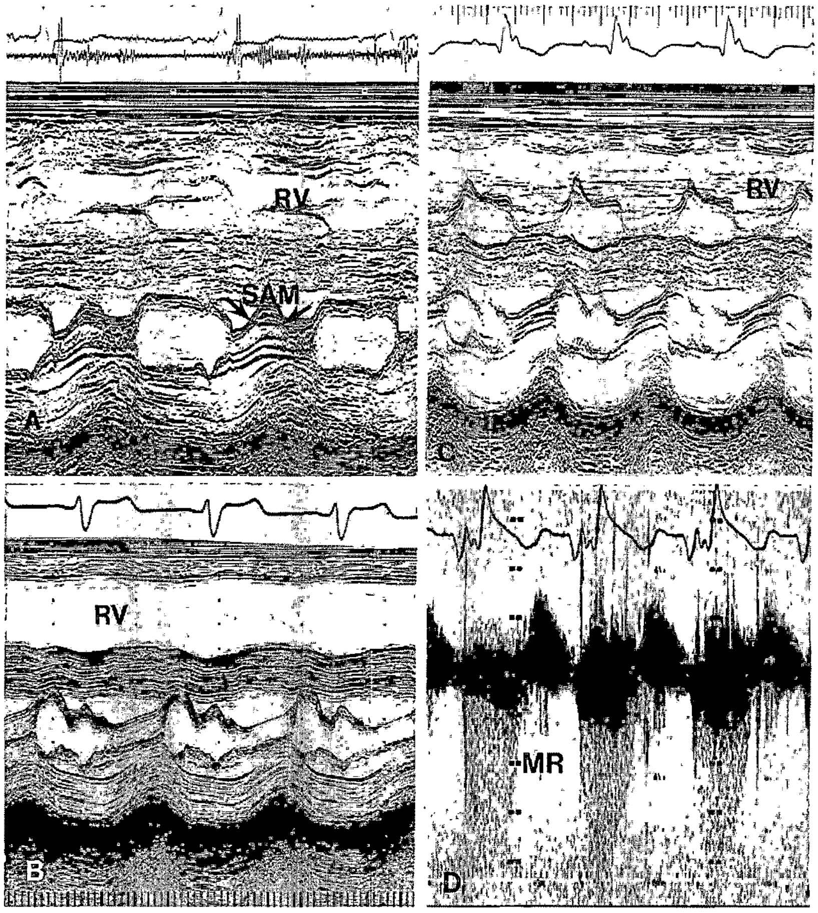

FIGURE 1. M-mode echocardiograms from patient 2 (CW). *A*, preoperative. Systolic anterior motion (SAM) of the mitral valve with mitral valve–septal contact. *B and C*, 6 and 25 months after septal myotomy-myectomy operation. SAM is now absent and the ventricular septum is thinner. *D*, postoperative. Continuous-wave Doppler tracing obtained from left ventricular apex showing mitral regurgitation (MR). RV = right ventricle.

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TABLE I Observations in Three Patients with Hypertrophic Cardiomyopathy Who Had Ventricular Myotomy–Myectomy for Left and/or Right Ventricular Outflow Obstruction Followed Later by Mitral Valve Replacement for Pure Mitral Regurgitation

	Patient 1 (MS)				Patient 2 (CW)				Patient 3 (AM)			
	Before M&M	Six Months After M&M	Shortly Before MVR	Six Months After MVR	Before M&M	Six Months After M&M	Shortly Before MVR	Six Months After MVR	Before M&M	Six Months After M&M	Shortly Before MVR	Six Months After MVR
Age (years)	23	23	34	34	22	22	24	25	55	55	60	60
Functional class (I–IV) (NYHA)	3	1	3	2	3	2	3	2	4	2	4	2
Atrial fibrillation	0	0	0	0	0	0	0	0	+	+	+	+
Echocardiographic findings												
Systolic anterior motion	+	–	0	–	+	0	0	–	+	0	0	–
Right ventricular cavity (mm)	28	–	35	34	30	36	42	40	22	30	29	28
Left atrial cavity (mm)	56	–	66	64	46	55	55	60	45	50	62	57
Left ventricular cavity (mm) (s/d)	38/–	–	50/38	50/40	31/21	41/24	46/34	45/	38/24	42/32	42/30	44/32
Ascending aorta (mm)	33	–	32	32	26	28	29	–	25	25	28	29
Ventricular septum (mm)	21	–	10	10	34	19	14	–	21	11	12	12
Left ventricular free wall (mm)	14	–	14	14	18	18	18	–	10	10	10	10
Intravascular pressures (mm Hg)												
Pulmonary artery wedge, V (m)	12 (9)	14 (11)	26 (18)	10 (7)	20 (15)	36 (29)	–	–	25 (18)	–	30 (24)	32 (21)
Right ventricle (s/d)	28/6	26/6	33/7	26/9	95/18	56/24	–	–	48/4	–	65/12	67/18
Pulmonary artery (s/d)	26/18	26/10	33/12	26/4	34/24	57/29	–	–	48/20	–	65/30	67/25
Left ventricle (s/d)	90/13	110/28	93/22	95/6	125/20	102/37	–	–	150/6	–	122/17	115/16
Aorta (s/d)	90/55	120/60	93/57	100/58	125/78	115/75	–	–	96/60	–	122/60	120/60
LV–aorta peak systolic gradient												
Rest	0	0	0	0	0*	0	–	–	54	–	0	0
Provocation	91	0	0	0	70	0	–	–	96	–	–	0
Cardiac index (liters/min/m²)	2.9	2.9	1.7	2.6	2.9	1.8	–	–	1.9	–	2.7	1.7
Mitral regurgitation (0.4+), LV cine	1+	–	4+	1+	3+	3+	3+	–	2+	–	3+	0
Interval (mo) M&M to MVR		128			├──		25 ──┤		├──	73	──┤	
Interval (mo) MVR to March 1990				44			├──	21 ──→			├──	97‡ ──→
Date of M&M (month–year)	11–1975	–	–	–	6–1986	–	–	–	2–1976	–	–	–
Date of MVR (month–year)	–	–	7–1986	–	–	–	6–1988	–	–	–	2–1982	–
Type (size [mm]) substitute valve	–	–	B-S (27)	–	–	–	SJM (31)	–	–	–	Hancock (27)	–
Operative findings												
Weight VS excised (g)	9.6	–	–	–	10.2†	–	–	–	0.6	–	–	–
Ruptured mitral CT	–	–	+	–	–	–	0	–	–	–	0	–
Prolapsed PML	–	–	0	–	–	–	0	–	–	–	+	–
Thickened AML + CT	–	–	+	–	–	–	+	–	–	–	+	–

*Immediately before provocation, peak systolic gradient at rest was 50 mm Hg. Note that this patient had a 61 mm Hg systolic pressure gradient at rest between right ventricle and a major pulmonary artery.

†Includes myocardium from both right and left ventricular outflow tracts.

‡This patient died suddenly 97 months after mitral valve replacement. A necropsy was not performed.

AML = anterior mitral leaflet; B-S = Bjork-Shiley prosthesis; cine = cineangiography; CT = chordae tendineae; LV = left ventricular; M&M = myotomy and myectomy (partial); MVR = mitral valve replacement; NYHA = New York Heart Association classification; PML = posterior mitral leaflet; s/d = peak systolic/end diastolic; SJM = St. Jude Medical prosthesis; V = peak V wave; VS = ventricular septum; – = no information available or not done.

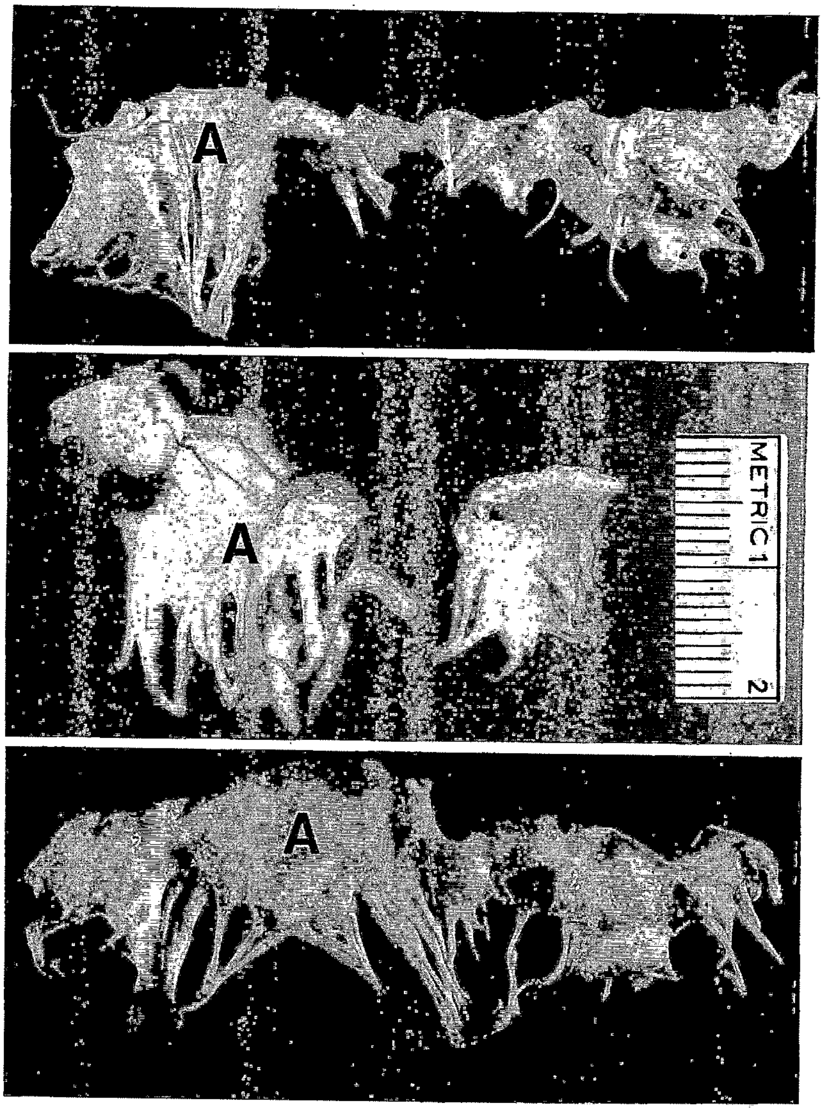

FIGURE 2. Operatively excised mitral valves from each of the 3 patients. *Upper,* patient 1 (MS) showing ruptured chordae tendineae from the anterior half of the anterior (A) mitral leaflet. A portion of the posterior leaflet is elongated. *Middle,* patient 2 (CW). Chordae from the anterior (A) half of the anterior leaflet also are absent (ruptured). *Bottom,* patient 3 (AM). No chordae are ruptured or missing but a portion of posterior leaflet is elongated. The *bottom* photograph is reproduced with permission from the American Heart Association, from Maron BJ, Harding AM, Spirito P, Roberts WC, and Waller BF. Systolic anterior motion of the posterior mitral leaflets: a previously unrecognized cause of dynamic subaortic obstruction in patients with hypertrophic cardiomyopathy. *Circulation* 1983;68:282–293.

ened by 1 New York Heart Association functional class in patients 1 and 2 and by 2 functional classes in patient 3 late postoperatively.

Almost every patient who undergoes ventricular septal myotomy-myectomy for left ventricular outflow obstruction has some degree of mitral regurgitation preoperatively. This operative procedure usually reduces the degree of mitral regurgitation, and it also usually relieves left ventricular outflow obstruction.[3] Reoperation is seldom necessary in obstructive hypertrophic cardiomyopathy and when it is performed, the indication is usually persistent left ventricular outflow obstruction. Rare is the postoperative patient who has pure mitral regurgitation producing significant symptoms without any associated left ventricular outflow obstruction. Such was the case, however, in our 3 patients.

The causes of the worsening or persistence of pure mitral regurgitation in patients 1 and 2 appear to have been inadvertent severance of several mitral chordae tendineae at the time of the myotomy-myectomy operation. This technical complication was unrecognized at operation. Retrospective review of the intraoperative echocardiogram before and after the septal myectomy, however, clearly indicates that several chordae tendineae were severed. Patient 3 was known to have systolic anterior motion of a portion of posterior mitral leaflet before myotomy-myectomy and this systolic anterior motion persisted after the initial operation. Why the mitral regurgitation worsened, however, after relief of left ventricular outflow obstruction was not discernible from study of the operatively excised mitral valve.

This study indicates that damage may occur to the mitral valve at the time of ventricular septectomy-septotomy in obstructive hypertrophic cardiomyopathy, and that this damage may cause worsening of or persistence of mitral regurgitation postoperatively.

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Alkaline Paper and Preserving the Record

The paper used for articles published in many of our major medical journals including *The New England Journal of Medicine*, *The Journal of the American Medical Association*, *Circulation*, *The American Heart Journal*, and *The American Journal of Cardiology* is acidic, and, therefore, these pages will crumble and blow away as dust within 50 years.[1-4] * In contrast, if these journals had been published on acid-free (alkaline) paper, the articles would be preserved for 500 years, maybe longer, depending on how they were stored. So why do these journals which record our scientific record use the non-permanent paper?

Magnitude of the problem: Nearly 80 million books in North American research libraries and an estimated 1,000 million books in libraries worldwide are threatened with destruction because they were printed on acidic paper.[1-4] In most university libraries in the USA about 30% of the volumes are brittle such that just 1 reading or 1 xerographing or 1 microfilming of the pages causes them to shatter irreparably. At the New York Public Library over 35 of 88 miles of bookshelves contain over 2.5 million dying books.[4,5] An estimated 25% of the 24 million books in the Library of Congress are not circulated because the pages crack when folded, and every year 77,000 more books in the collection become equally brittle.[4] It is estimated that 97% of the volumes in the federal government's premier library—which not only houses the largest collection of our English language heritage but also that of Latin America and the Arab world—will eventually disintegrate. The collection of the National Library of Medicine, the world's largest research library in a single scientific and professional field, contains 4.5 million items—books, journals, technical reports, manuscripts, microfilms and pictorial materials—and about 158,000 (12%) print volumes are brittle.[2,3,4,6] It is estimated that 92% of the post-1800 holdings of the library were printed on acidic paper. Seventy percent of books and journals printed in the twentieth century will be unusable by the year 2000.[4]

Origin of the acid in the paper: The oldest materials in libraries and archives are not the most endangered ones because acid was not introduced into the paper-making process until about 1850. Before that time linen and cotton rags were beaten by hand in water and the separated fibers collected on wire frame molds to make individual sheets of paper which were virtually devoid of acid.[7,8] With the coming of the industrial revolution and the increase in literacy in the mid-nineteenth century, the demand for paper skyrocketed. The result was that the hand-processed rag stock was largely abandoned in favor of wood pulp churned out by newly perfected machines. The wood pulp was of 2 types. *Mechanical* wood pulp is that produced by grinding up logs or shredding and grinding wood chips.[4] This type of pulp contains lignin, which is the primary non-cellulosic component in trees, and it causes paper to darken upon exposure to light and to degrade relatively quickly by oxidation and hydrolysis. (Newsprint has a high lignin content.) Because mechanical wood pulp contains lignin and other impurities, paper containing it has a relatively short lifespan. *Chemical* wood pulp is pulp produced by cooking wood chips in chemicals (to remove impurities).[4] Depending on what chemicals are added in subsequent processing, the resulting paper can be either acidic and have a relatively short shelf life, or alkaline and have a long shelf life. Unfortunately, until recent years, the most common chemical added was aluminum sulfate, an acid salt. Not until the late 1930s was it discovered that it was the acid, primarily sulfuric acid derived from the aluminum sulfate or alum, in the paper that caused it to be unstable and to degenerate. Already by 1910, however, it was learned that papers containing alkaline fillers, calcium carbonate for example, were quite stable and therefore permanent.[4]

Preservation of the deteriorating acidic publications: Preservation of the present print heritage is the major problem facing most libraries today.[1-3] During the next 10 years The National Library of Medicine is expected to invest the equivalent of one third of its acquisition budget to "clean up" the backlog of embrittled material. Microfilming of the brittle books, which costs about $70 a volume, is about the only currently available recourse but this process does not save the book. Currently, The National Library of Medicine is microfilming 20,000 to 25,000 volumes a year as part of its preservation program. Another preservation technique, which also treats one book at a time, consists of placing the book in a water-based solution, but this technique requires removal of the book's binding and is even more expensive than microfilming. In yet another process, which takes

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*The *Annals of Internal Medicine* switched to alkaline paper on November 1, 1991. The printer of the journal switched from acid to alkaline paper at no additional charge to the journal.

hours, each page is sprayed by hand with a base that neutralizes the acid. Several companies are trying to develop affordable techniques that rely on either a liquid or a vapor to treat hundreds of books at a time.[4,9,10] The books are immersed in a bath of magnesium butoxytriglycolate or some like substance, then drained, rinsed with a solvent, and dried again. The process theoretically neutralizes the acid and then the paper is treated with a buffering agent that bonds broken fibers and, therefore, strengthens the brittle pages. Books may be impregnated in a large chamber using gases such as diethyl zinc or ethylene oxide as deacidifying agents. So far, the Library of Congress has not been convinced that these "dry cleaning" processes for books are reliable or effective. Electronic document storage and retrieval using digital optical discs as the storage medium is being developed, but thus far this method of preserving the record is not ideal. Most discs have a lifetime of about 10 years, shorter than that of acid paper![11]

Prevention of deterioration of future print publications: The prevention of future paper embrittlement is actually easy The answer is simply to use acid-free (alkaline) paper for all future publications.[1–4] In actuality, tremendous progress is being made rapidly toward that goal. In January 1987 the first meeting took place of The National Library of Medicine's Permanent Paper Task Force consisting of 34 members representing publishers, paper manufacturers, printers, editors, writers, and librarians. I was pleased to be the only physician on that task force. In January 1987 only 4% of the 3,050 titles of *Index Medicus* were published on acid-free paper. By October 1991 the time of the most recent meeting of the Permanent Paper Task Force, 48% of the titles of *Index Medicus* were known to be published on acid-free paper! In 1987 acid-free paper was in short supply and 2 manufacturers had a virtual monopoly on it in North America. Now, an estimated 35 paper manufacturers provide acid-free paper, such that today it is probably easier to purchase acid-free paper than acid paper. It is estimated that slightly over 50% of the paper produced for US print is now on alkaline paper. The expense of lost production is the biggest cost in conversion from acid to acid-free paper making. Conversion can vary from days to weeks among paper producers. Once the conversion is made it is cheaper to produce the alkaline paper than the acid paper. The reason is because calcium carbonate is cheap and larger quantities of this type of filler can be used than the more expensive filler used in acid paper. The alkaline papermaking process also requires considerably less water than does the process for acidic paper, and therefore the amount and need for treatment of discharge from mills into streams and rivers is drastically reduced. Alkaline paper making also is cleaner and less corrosive to machinery than acid-based paper making. Alkaline paper is an important marketing tool for both paper manufacturers and publishers. Alkaline paper is smoother and stronger than acidic paper, and type printed on it is usually sharper and easier to read than type on acidic paper. And shattering a commonly held belief, acid-free paper is price comparable in quality weights and grades to acidic paper.

Another factor pushing conversion toward alkaline paper is the increased sensitivity or awareness of the problem by paper producers, publishers, and authors. About 3 years ago I was asked to serve as a consultant to a new publishing company of medical books. I mentioned to the publisher that I would be glad to serve as a consultant but only if the books were to be published on acid-free paper. He asked "what was acid-free paper?" and what were its advantages over other paper? I was surprised to learn that he had never heard of acid-free paper. Four years ago I was talking to a publishing executive of the only USA cardiology journal published on acid-free paper. He had become aware only a month or so earlier that his journal was published on alkaline paper. It so happened that all journals published by that particular publisher used acid-free paper.

Authors are becoming progressively more sensitive to the problem. In March 1989 nearly 100 distinguished authors and major publishing figures gathered at the New York Public Library to pledge their commitment to the preservation of the printed word.[12] They signed a landmark declaration of book preservation calling for the use of acid-free paper for all first printings of quality hard-cover trade books. The declaration was signed at a special program entitled "Commitment Day" which was spearheaded by author and library trustee Barbara Goldsmith who has been galvanizing the literary community for this national preservation effort.

A major impetus toward conversion to acid-free paper has come from the federal government of the USA. In October 1990 the 101st Congress passed Public Law 101-423, which requires "the use of acid free permanent papers for publications of enduring value produced by the Government Printing Office or produced by Federal grant or contract. . . ."[4] This law has had a rapid impact on paper producers in North America because of the enormity of the USA's governmental printer. The Government Printing Office publishes 60,000 titles a year, a total valued at 1 billion dollars. The government's printer uses 500,000 tons of paper annually, an amount equivalent to 2.2% of all printed paper in the USA. In 1991, 77% of the paper used by the Government Printing Office will be alkaline and by 1996, 100% of the paper it uses will be alkaline. A good portion of this paper is of the recycled type and recycled and new alkaline paper is indistinguishable.

One item in Public Law 101-423 was the following[4]: "The Congress of the United States urgently recommends that American publishers and state and local governments use acid-free permanent papers for publications of enduring value. . ." Since passage of the federal law at least 21 states in the USA have passed similar laws or resolutions in their state houses, a move further pushing paper manufacturers in the USA to rapidly move from producing acid paper to alkaline paper. It is expected that most of the remaining states will pass similar laws or resolutions in the next few years.

Another item in Public Law 101-423 was the following[4]: "The Congress of the United States urgently recommends that the Secretary of State, Librarian of Congress, Archivist of the United States and other officials make known the national policy regarding acid free permanent papers to foreign governments and appropriate international agencies since the acid paper problem is worldwide and essential foreign materials being imported by our libraries are printed on acid paper." Europe began the move toward using alkaline paper about 20 years ago and thus is far ahead of the USA in publishing on alkaline paper. Virtually all paper produced in the 5 Scandinavian countries is now alkaline. Several other European countries as well as Canada and Australia are developing permanent paper standards.

Identifying publications using permanent paper: It is important that the use of permanent paper for a publication be identified by a notice on the verso of the title page of a book or in the masthead or copyright area of a periodical.[4] Such identification attests to the concern of the publisher and the author(s) for the preservation of the material published. Without it, libraries would have to test each publication and may in the future inadvertently apply time-consuming and expensive preservation treatments to publications that do not need them. The National Information Standards Organization (NISO) was selected by the American National Standards Institute (ANSI) and it approved and published in 1984 permanent paper standards for non-coated paper. The standards included (1) a minimum pH of 7.5; (2) tear resistance; (3) fold endurance; (4) minimum alkaline reserve equivalent to 2% calcium carbonate, and (5) absence of groundwood pulp. The infinity symbol within a circle was chosen to indicate that paper in the publication meets all 5 requirements of the permanent paper standard (Figure 1). For publications on coated paper and on uncoated paper that have not been demonstrated to meet all 5 requirements of the standard, but are known to be at least acid-free and free of groundwood, the phrase "Printed on acid-free paper" would appear in the publications. The permanent paper standard of 1984 (NISO/ANSI Z39.48) is now being revised and the revised standard, which is scheduled to appear in 1992, is being expanded to apply to both coated and uncoated papers.

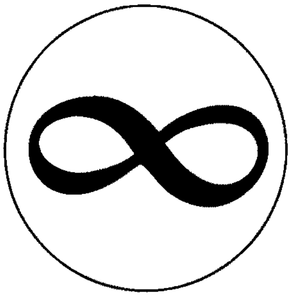

FIGURE 1. The infinity symbol within a circle should appear in all publications using alkaline paper and fulfilling 4 other criteria (see text).

Electronic publishing versus print publishing: There is a view that publishing in the foreseeable future will be by electronic means rather than by print means, and, therefore, it will not be necessary to preserve our previous print record or to prevent deterioration of our future print publications. Although electronics someday may be dominant, most experts today believe that paper publishing will remain the dominant type for many decades to come. The reasons are many. Paper publications are easy to read; they are highly portable; they are very comfortable to read; they are well accepted legally, and socially; they are durable (if published on alkaline paper); they can be published in a wide range of sizes, and they can accept advertising. In contrast, it is difficult to read to a grandchild from a screen. The electronic equipment is expensive. Advertising is difficult by electronic means. Databases are costly. There are legal problems in protecting the copyright because electronic publications are easy to copy. The quality of most electronic displays is not nearly as good as that of print publications. The user of electronic publications must be well trained in the use of the electronic equipment which rapidly becomes obsolete. So many people now use computers at work that it is nice to pick up a print publication when getting home. Thus, it is unlikely that electronic publishing will replace print publishing for years to come. Indeed, print publishing is increasing rather than the reverse. In 1990, an average of 320 pounds (145 kg) of printing and writing paper was used by each citizen in the USA, an increase from 308 pounds (140 kg) used in 1989, up again from the 294 (134 kg) pounds used in 1988.[6] At least 95% of all organizational records are estimated to reside on paper.[6]

Summary: The most productive period of human beings on planet earth has been the last 140 years (since 1850), and most publications during that period have been on acid paper and therefore they have or soon will vanish into dust. The next 140 years surely will be an even more productive period for humankind, and that record of accomplishment must be prevented from slowly burning into ashes. It is easy to prevent such an outcome. Simply printing our records on alkaline paper will allow our writings to remain permanently for future generations. A good quantity of toilet paper and paper towels now consists of acid-free paper. Surely if some of our toilet paper can be alkaline, most of our medical publications, including all our peer-reviewed journals, can use a paper of at least similar quality.

William C. Roberts

William Clifford Roberts, MD
Editor in Chief

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Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

LOPID®

BID

(gemfibrozil) 600-mg Tablets

RAISES HDL, LOWERS LDL AND TRIGLYCERIDES
DRAMATICALLY REDUCES HEART ATTACK

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available) 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.) *The Metabolic Basis of Inherited Disease,* 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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A powerful case for

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(gemfibrozil) 600-mg Tablets

LOPID is indicated for reducing the risk of coronary heart disease in type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid. LOPID is not indicated for the treatment of patients with low HDL cholesterol as their only lipid abnormality.

Reduced heart attack incidence up to 62%*

—in Helsinki Heart Study patients whose baseline HDL was < 35 mg/dL and median baseline LDL was 186 mg/dL.[1] Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).[1]

Raised low HDL 25%

—in these Helsinki Heart Study patients.[1]

Contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

*Defined as a combination of definite coronary death and/or definite myocardial infarction. P = .013, 95% CI 13 to 111.5

RAISES HDL, LOWERS LDL AND TRIGLYCERIDES
DRAMATICALLY REDUCES HEART ATTACK

Reference: 1. Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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